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Division of Research Resources

Program Highlights

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
Public Health Service
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Report of the Division Director

In Fiscal Year 1984 the budget of the Division of Research Resources (DRR) of the National Institutes of Health (NIH) was $243,177,000, from which the Division made extramural awards which totaled $236,324,506. This allowed DRR to meet its program commitments in full and continue its support of 166 major shared research resource centers throughout the United States.

The DRR awarded 965 research grants, 13 research training grants, and 3 research contracts in support of general clinical research centers (GCRC's), biomedical research technology resources, animal resources, minority biomedical research support, and the biomedical research support program. The number of DRR extramural research grants increased by 64 (7.1 percent) over 1983, while the dollar amount awarded increased by $29,129,000 (14.7 percent).

The DRR budget provided $81 million for continued support of 75 general clinical research centers; $47.1 million for 546 Biomedical Research Support Grant awards; $19 million for 115 Biomedical Research Support Shared Instrument Grants; $26.3 million for 47 biomedical research technology resource centers; $28.8 million for 44 laboratory animal science centers and primate research centers, of which $1 million was used for repair and renovation of the primate centers; and $21.8 million for 79 Minority Biomedica Research Support awards.

The table below provides a breakdown of funding to the DRR's five programs: the General Clinical Research Centers Program, the Biomedical Research Technology Program (formerly called the Biotechnology Resources Program), the Animal Resources

Division of Research Resources FY 1984 Overview of Extramural Activities

Program	Funding	Major Resources Supported
General Clinical Research Centers Program	$81,679,464	• 75 general clinical research cente • 48 Clinical Associate Physicians • 37 CLINFO awards
Biomedical Research Technology Program	$33,434,455	• 47 biomedical research technolog resource centers • 3 contracts, including the PROPHE computer network • 13 resource-related research project grants • A small grants program
Animal Resources Program	$31,434,588	• 7 primate research centers • 37 animal resource grants • 14 resource-related research project grants • 5 special emphasis research caree awards in laboratory animal sciences • 13 research training programs
Biomedical Research Support Program	$67,897,000	• Biomedical Research Support Grants awarded to 546 institutions • 115 shared instrumentation award • Minority High School Research Apprentice Program made 284 awards to support 666 students
Minority Biomedical Research Support Program	$21,878,999	• 79 MBRS awards
Total, Extramural	$236,324,506[a]	

[a]Excludes $1,486,272 of reimbursable authority from other Federal agencies

Program, the Biomedical Research Support Program, and the Minority Biomedical Research Support Program.

By the end of the Fiscal Year 1984, CLINFO, a data analysis system for clinical investigators, had been established at 38 locations, serving 46 of the General Clinical Research Centers (GCRC's). An electronic mailnet, which the CLINFO II advisory committee recommended, was initiated on an experimental basis, first between Duke University and the University of Cincinnati, and then extended to six additional CLINFO sites. The trial is continuing, with an eye to more widespread application should the results warrant.

During the past year, assessments of the condition of physical facilities at all seven of the now 25-year-old primate research centers revealed the need for extensive plant renovations and repairs and for replacement of major equipment items. A special Congressional earmark in Fiscal Year 1984 enabled DRR to begin to address these important needs at centers. The funds ($1 million) have allowed some of the centers' highest priority repair and renovation requirements to be met.

The breeding of endangered and scarce primate species at the primate centers continued during the year. Although this effort often represents a burden on scarce resources, it is worthwhile because the number of primate species available in the world is shrinking rapidly as a result of habitat loss to agriculture.

An evaluation, conducted under contract with the National Academy of Sciences (NAS), was begun on the relevance and limitations of the use of cell systems, lower organisms, and nonbiological systems as models in biomedical research. If the results of the study indicate a need, an extramural grants program in Biomedical Research Model Development will be initiated.

An evaluation of the Biomedical Research Support Grant (BRSG) Program was conducted in Fiscal Year 1984. Among the conclusions of the study were: that the BRSG Program funds were reaching the institutional programs, departments, and investigators for which they were intended, and, as far as the study could determine, were resulting in impressive benefits; that the BRSG funds were highly valued by both investigators and administrators because of their flexibility and the institution's ability to administer them on a quick turn-around basis.

Fiscal Year 1984 marked the third year of operations for the BRSG Shared Instrumentation Grant Program. From its beginning in 1982 support for the program has grown steadily from $3.7 million to $19.7 million in Fiscal Year 1984. Because of budget increases, the number of awards for large-scale instrumentation shared among individuals, research groups, departments, and institutions expanded from 23 in 1982 to 115 in 1984.

Plans for the future of the Biomedical Research Technology Program PROPHET Computer Resource were developed during the year. A PROPHET Advisory Panel was assembled to provide the Program advice on future directions for PROPHET. As a result of the Panel's recommendations, a Request for Proposal for redevelopment of PROPHET's software and hardware was issued; a contract for PROPHET II, the second generation network, is expected to be awarded during Fiscal Year 1985.

FY 1984 Awards by Program Component as a Percentage of Total DRR Extramural Support
(Including Research Grants, Research Training Grants, and R & D Contracts)

GCRCP—General Clinical Research Centers Program 34.6%
BRTP—Biomedical Research Technology Program 14.1%
ARP—Animal Resources Program 13.3%
BRSP—Biomedical Research Support Program 28.7%
MBRSP—Minority Biomedical Research Support Program 9.3%

About 1,500 student and faculty participants in the Minority Biomedical Research Support Program gathered in Washington, D.C., in mid-April for the 12th Annual MBRS Symposium. The students presented 570 papers and poster displays. Both faculty and students engaged in workshops on electron microscopy and high-performance liquid chromatography. Minisymposia and lectures on "Nutrition and Aging," "Hypertension," and "AIDS" also were attended by interested students and faculty.

On the basis of extensive consultation, including the Fiscal Year 1983 NARRC-sponsored retreat, the Minority Biomedical Research Support Program developed two new initiatives for 1985. One initiative focused on biomedical research participation by undergraduate colleges that have substantial enrollments of minority students and are not currently funded by the MBRS Program. The other is designed for minority institutions with more biomedical research faculty and updated research equipment which are capable of developing greater faculty and interdepartmental collaboration around specific research themes or disciplines. This "Thematic Project Grant," a new type of MBRS award, is planned as another transitional step toward regular NIH grant support.

Three meetings of the National Advisory Research Resources Council took place during the year with major presentations on the Biomedical Research Technology Program, Technology Assessment at NIH, and DRR Budgetary Trends. Regular meetings of the DRR's research review/advisory committees (GCRC, BRTP, BRSG, and MBRS) took place along with workshops on special topics including the PROPHET Colloquium, MBRS Grantsmanship Workshop, Future Directions in Electron Microscopy, and Viral Infections of Laboratory Rodents. In addition, meetings were held by Program Directors of several of the programs, including the GCRC and the MBRS Program Directors, and the Directors of the Primate Research Centers. The DRR Director participated in most of these activities.

Among significant communications activities for Fiscal Year 1984, the Division's Office of Science and Health Reports planned, coordinated, and participated in eight special events, including General Clinical Research Center 20th anniversary celebrations, press briefings, and dedications. The DRR Director participated in most of these events, presenting a commemorative plaque to the principal investigator on each of these special occasions. Dr. James Wyngaarden, Director of NIH, spoke on "New Challenges in Outpatient Research and Training" at the dedication of the University of Texas Health Science Center, Dallas, GCRC Outpatient Unit. Noted National Institute of Mental Health neurologist Dr. Louis Sokoloff delivered a lecture entitled "Visualization of Brain Function" to dedicate the Laboratory of Neuro-Imaging at Washington University; the laboratory was funded under a DRR Shared Instrumentation Grant. The National Center for Biomedical Infrared Spectroscopy of Battelle Laboratories, Columbus, Ohio, supported by the Biomedical Research Technology Program, was dedicated by Dr. William F. Raub, NIH Deputy Director for Extramural Research and Training, who spoke on "Funding Trends in Biomedical Research." At the 20th anniversary celebration of the University of Tennessee Center for the Health Sciences GCRC, Dr. Doris Merritt, special assistant to the NIH director, spoke on medical training and clinical research. Other GCRC 20th anniversary celebrations were held at the University of California, San Francisco, and at the Medical College of Wisconsin. At the GCRC of the University of Texas Health Science Center, Dallas, a press briefing was held on potassium citrate, an orphan drug present in citrus fruits which is used to treat kidney stones. Scientists from the University of Washington Medical Center and the Regional Primate Research Center in Seattle held a media briefing on an improved cochlear prosthesis that was about to be clinically tested.

During the year, the Division's publications, produced through its Office of Science and Health Reports and its Research Resources Information Center, won four awards, including the first presentation of the Eric Martin Award of the American Medical Writers Association for the best article, brochure, or monograph on therapeutic or pharmaceutical services. The award went to "Monoclonal Antibodies Against Cancer: Clinical Application" published in the *Research Resources Reporter.* Other awards came from the Health Sciences Communication Association and the National Association of Government Communicators.

In the following sections of this survey of the DRR's activities, detailed descriptions are given of the mission, the scope of support, and important accomplishments of each program during 1984.

Betty H. Pickett, Ph.D.
Director, Division of Research Resources
National Institutes of Health

General Clinical Research Centers Program

Program Description

The General Clinical Research Centers (GCRC) Program has been in operation since 1959 and provides resources for 75 GCRC's where highly qualified investigators have the opportunity to advance the knowledge of medicine in a clinical setting. Between the time of the initial center grant award in 1960 and Fiscal Year 1984, the program has maintained support for a dynamic cadre of clinical investigators.

Specific goals of centers funded by the Program are:

- ☐ to learn more about normal and abnormal body function and about the cause, progression, prevention, control, and cure of human diseases;
- ☐ to provide an optimal setting for controlled investigation by clinical scientists supported by the NIH and other organizations;
- ☐ to encourage increased collaboration among investigators in the basic and clinical sciences;
- ☐ to encourage, develop, and maintain a national corps of expert clinical investigators; and
- ☐ to provide resources that allow advances in basic scientific knowledge to be translated into methods for improved patient care.

The contributions of GCRC research to improved patient care are numerous. Current studies range from improvements in treating high blood pressure to the detection of hereditary diseases by genetic markers. Research projects conducted at the clinical research centers are funded by the individual institutes of the NIH, by other agencies of the Department of Health and Human Services, by research foundations and societies, and by industry.

In 1984 the GCRC's provided the specialized environment needed to conduct clinical research for more than 3,800 projects. Here a GCRC researcher measures the level of glycosylated hemoglobin, an indicator of how well blood glucose levels are controlled among diabetic patients.

Conducting a successful clinical research protocol is highly dependent on the research setting. Thus, the centers are designed to provide the best possible environment, including the personnel and the technical tools, in which researchers can provide superior care for research patients while acquiring new health knowledge.

The research capacity of the 75 centers in the GCRC Program is equivalent to that of a single 600-bed hospital devoted entirely to clinical studies. The centers accommodate both inpatients and outpatients, providing the specialized care needed for studies on both adults and children. In 1984, 88 beds were on pediatric wards or in children's hospitals. Of the 75 centers, 66 admit pediatric patients on a regular basis. One center is devoted to research on maternal and fetal problems surrounding delivery; another is dedicated to research involving premature infants. One center is involved entirely in outpatient research, and one is dedicated to dental problems.

During the 24 years of the GCRC Program's operation, use of the research beds has become more efficient; fewer beds are supported, inpatient stay is shorter, and more scientific publications are produced. A considerable share of the research is now conducted on outpatients. The cost to DRR of operating the centers is reduced by third-party reimbursements for the necessary hospitalization costs of one-third of the patients. The well-accepted and highly successful CLINFO system for rapid, computerized handling of clinical research data is now supported at 46 centers. Core laboratories continue to be an integral part of the resources supported, and some have newly acquired sophisticated equipment such as mass spectrometers. Finally, efforts have increased in recent years to develop formal evaluations of the program's contributions to specific advances in medicine.

A typical clinical research center can accommodate both inpatients and outpatients and supports 1 or 2 medical program directors, 12 nurses, 3 dietitians, 2 laboratory technicians, and administrative personnel.

The average center size is about 8 beds, although they range from 4 to 30 beds. Centers often contain treatment rooms, a core laboratory, a diet kitchen, patients' lounge space, a nurses' station, a conference room, and outpatient space. The GCRC Program pays the hospital costs of the patients admitted to the center solely for research purposes. About 35 percent of patients participating in research projects require hospitalization for diagnosis or treatment; these patients are billed for that portion of their care, usually through third-party insurers.

Technical advances in balloon catheterization have enabled researchers to open totally blocked arteries. The new technique may be an alternative for some patients who would otherwise need coronary bypass surgery, according to a study conducted at the Beth Israel Hospital GCRC in Boston.

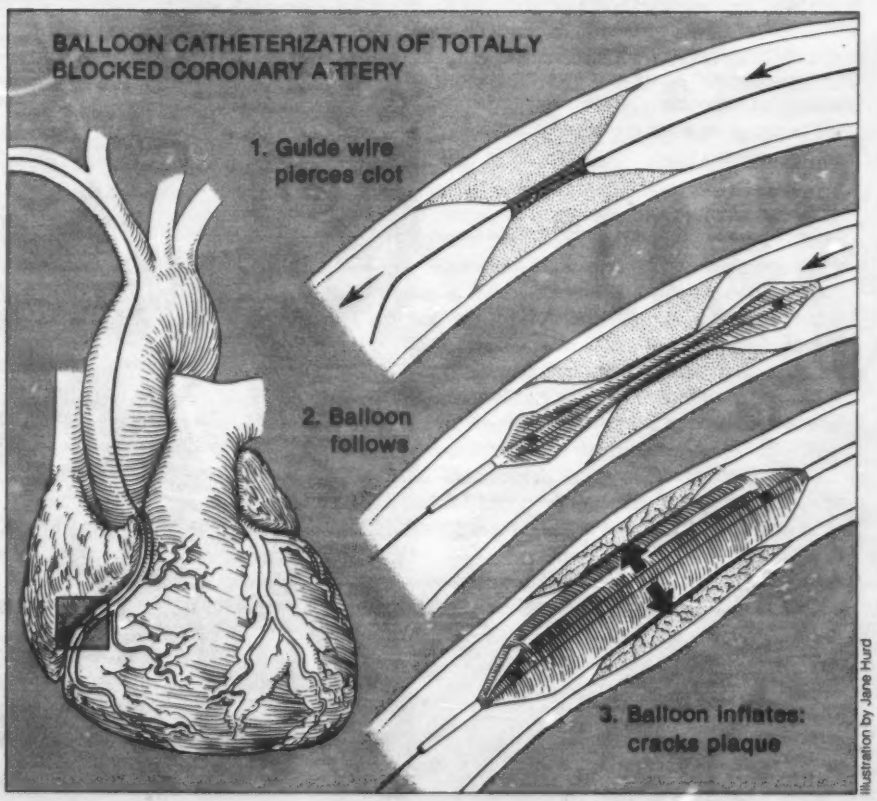

BALLOON CATHETERIZATION OF TOTALLY BLOCKED CORONARY ARTERY
1. Guide wire pierces clot
2. Balloon follows
3. Balloon inflates: cracks plaque

Illustration by Jane Hurd

When patients require routine tests at a clinical research center, the hospital's clinical laboratory often handles them. But because standard hospital laboratories cannot always provide routine tests and assays with the speed or accuracy clinical investigators need, these are sometimes provided by the core laboratory. The kinds of tests core laboratories perform vary from center to center, depending on the requirements for core services. Often they are sophisticated, state-of-the-art tests needed for clinical research by a number of center investigators but not yet available through the hospital laboratories.

The metabolic kitchen is a center component essential for maintaining its controlled environment. It provides a level of dietary control not available elsewhere in the hospital.

Among the most important elements of a center are its highly trained paramedical personnel. Nurses, dietitians, laboratory workers, and other support personnel, trained in the methodology of clinical research, perform duties essential to maintaining high clinical research standards.

Average GCRC (8 beds) Funded in FY 1984

Personnel	Full-Time Positions	Dollars
Professional	1.1	82,000
Administrative	1.4	32,000
Laboratory	2.4	55,000
Dietary	3.2	54,000
Nursing	11.6	276,000
Other*	1.3	33,000
Fringe benefits		120,000
Subtotal	21.0	657,000
Hospitalization		303,000
Travel		3,000
Supplies, equipment, other		112,000
Indirect costs		87,000
Total		1,162,000

*Includes CAP's.

Program Highlights

During 1984 the centers continued to improve clinical data management capabilities, increase clinical research training, and update technology in the core laboratories. The GCRC Program support of clinical research centers, the Clinical Associate Physician (CAP) Program, and CLINFO awards totaled $81,679,464.

Fifteen new CLINFO awards began in 1984, so that a total of 37 CLINFO sites serving 46 centers were operating. The CLINFO system can analyze data for as many as 5,000 patients per study, a capability large enough to accommodate most clinical trials. An analysis of CLINFO among 19 centers during 1984 showed that investigators used 74,848 connect hours. CLINFO was used in the preparation of 610 GCRC publications and 362 abstracts during the year. It was supported by $6,033,627 of GCRC Program funds.

The postfellowship CAP Program provided 38 physicians with grants and other support for clinical research. A significant decline in the number of young physicians entering biomedical research a decade ago and a decrease in subspecialty training fellowships prompted the GCRC Program to start the CAP Program in 1974. The program, which provides postfellowship salary support, is designed to sponsor young medical scientists at the beginning of their careers in clinical investigation. Through 1984, 109 CAP's had been funded and half of the CAP graduates in U.S. academic centers had obtained NIH support for their clinical research investigations.

The GCRC Program collaborated with DRR's Minority Biomedical Research Support Program to develop a small clinical research center at Meharry Medical College, a predominantly minority institution.

Each GCRC may use up to $3,000 of its awarded funds for stipends to medical students who conduct research at the centers. The stipends help expose young people to clinical research early in their careers, hopefully fostering a lifelong interest in this area. Twenty-seven medical students at 16 GCRC's in 1984 took advantage of this research opportunity.

The GCRC's continued to provide key resources for research supported by grants from the NIH categorical institutes. In 1984 the GCRC specialized environment was used by 4,659 investigators to study 3,831 research projects covering the spectrum from cancer,

diabetes, and hypertension to genetic and neurological diseases. A selected bibliography of research articles published by GCRC investigators has been compiled. Special reports have been prepared to document advances in hypertension, aging, arthritis, treatment of digestive and genetic diseases, and maternal and child health achieved by investigators who have conducted research in GCRC's with support grants from the several institutes of NIH. Research at GCRC's in these and other areas is highlighted in the following paragraphs.

Hypertension and the Heart

Balloon Catheterization May Be Alternative to Bypass Surgery. Advances in balloon catheterization—the use of tiny balloons to open clogged arteries—have enabled researchers at Beth Israel GCRC in Boston to disperse plaque and reopen totally blocked coronary arteries in 31 of 45 patients in a study group. The procedure, which may be an alternative for cardiac bypass surgery in some patients, had previously been restricted to people with narrowed, rather than totally blocked arteries. In practice, researchers insert a catheter into the femoral artery of the patient's thigh. A flexible wire is carefully threaded through until it penetrates the blockage in the coronary artery. Then a balloon is slipped over the wire and inflated, stretching the blocked artery and cracking the plaque so it can be absorbed in the bloodstream. Although the opened artery may narrow in some patients, the procedure can be repeated. Total reclosure of an artery following the balloon procedure occurs in only about 3 percent of the patients and may not be damaging to those who had a totally blocked artery to begin with. Many such patients have highly developed collateral arteries that can meet the blood and oxygen demands of the heart if the artery closes. In contrast, patients who have only a partial blockage may require emergency treatment if there is a sudden closure. The researchers predict that the balloon method will probably become a routine procedure for the majority of people with totally blocked arteries.

Heart Disease and Smoking. Cigarette smoking has for years been linked to an increased risk for heart disease, and a recent study at the Oregon GCRC in Portland suggests a possible cause: smoking appears to increase plasma levels of triglycerides and very-low-density lipoproteins and to decrease the supply of high-density lipoproteins (HDL). Low levels of HDL and high levels of triglycerides are known to be major risk factors for cardiac disease. In the GCRC study smokers had significantly lower levels of HDL than people who had quit smoking or had never smoked. Adverse effects were most pronounced in heavy smokers. Those subjects who smoked more than 15 cigarettes a day had the fastest heart rates and the highest levels of total plasma cholesterol and triglycerides and the lowest levels of HDL. The subjects, who ranged from age 16 to 70 and included both men and women, were part of a 5-year Family Heart Study in which people gradually adapt to a low cholesterol, low fat diet. The GCRC researchers plan to investigate the link between smoking and other habits, including drinking alcohol or coffee.

Kidney Disease May Cause Hypertension. Replacing diseased kidneys with healthy ones and removing all atrophied tissue may reduce high blood pressure in some patients with essential hypertension, and reverse associated heart and retina damage. GCRC researchers at the University of Alabama in Birmingham and other scientists examined one group of patients an average of four years after they had received kidney transplants to relieve end-stage kidney failure caused by nephrosclerosis. All of the patients had previously suffered from hypertension, but blood pressure levels were normal during the followup examinations. The subjects also showed signs that related damage to the heart and blood vessels had reversed. But the same team in another study of patients with similar histories found that kidney transplantation alone does not always alleviate essential hypertension. Some patients from the second study, however, did achieve normal blood pressure after removal of atrophied kidneys that were not excised during the transplant. The researchers hypothesize that diseased kidneys adversely influence blood pressure, possibly through hormonal effects.

Advances in Hypertension. Because renal hypertension, especially renal disease caused by narrowed arteries, can be curable, diagnosis of the condition is under intense study. Diagnostic tests have been studied and devised at 14 GCRC's. The tests are performed in a prescribed sequence so that patients who do not have renal hypertension are spared the discomfort and expense of complex studies, while those who do have the disease are treated appropriately. The tests include a careful physical examination, searching for abdominal bruits or murmurs, measurement of the enzyme renin in the venous blood supply of both kidneys, and trial doses of certain drugs.

Coughing and the Heart. Forceful, repeated coughing may test a patient's capacity for

Photo courtesy of the Office of Information Services, University of Wisconsin-Madison

Kidney transplants may alleviate high blood pressure and reverse associated heart and retina damage in some patients with essential hypertension. Studies conducted at the GCRC of the University of Alabama in Birmingham and other clinical research centers indicate that removal of diseased kidney tissue in conjunction with the transplant of a healthy kidney may be most effective in achieving normal blood pressure.

cardioacceleration and the heart's ability to withstand stress, without the use of expensive and bulky diagnostic equipment. The heart rate of more than 250 healthy subjects, aged 18 to 90, rose an average of 31 percent when they coughed forcefully 3 times in 3 seconds from a resting position. The increase in heart rate appeared to lessen with age. GCRC researchers at Beth Israel Hospital in Boston hope to use the cough test to differentiate between healthy individuals and those with heart disease. Advantages of the simple, inexpensive test are that it can be performed at a physician's office or a patient's bedside and is easily repeatable. Data organization and analysis in the study were performed in part on the PROPHET system, a computer resource sponsored by the DRR Biomedical Research Technology Program; the subjects were members of a National Institute of Aging study.

Diabetes

New Evidence that Diabetes May Be an Autoimmune Disease. A group of diabetics who recently received pancreas transplants are providing physicians with new evidence for the theory that diabetes may be an autoimmune disease, occurring when the immune system mistakenly attacks the cells that produce insulin. A surgeon at the University of Minnesota Hospitals GCRC in Minneapolis tracked the progress of four long-term diabetics who had received insulin-producing pancreatic tissue implants from their healthy identical twins. Although the overall success rate for such surgery has only been about 25 percent since 1978, patients are more likely to accept genetically compatible

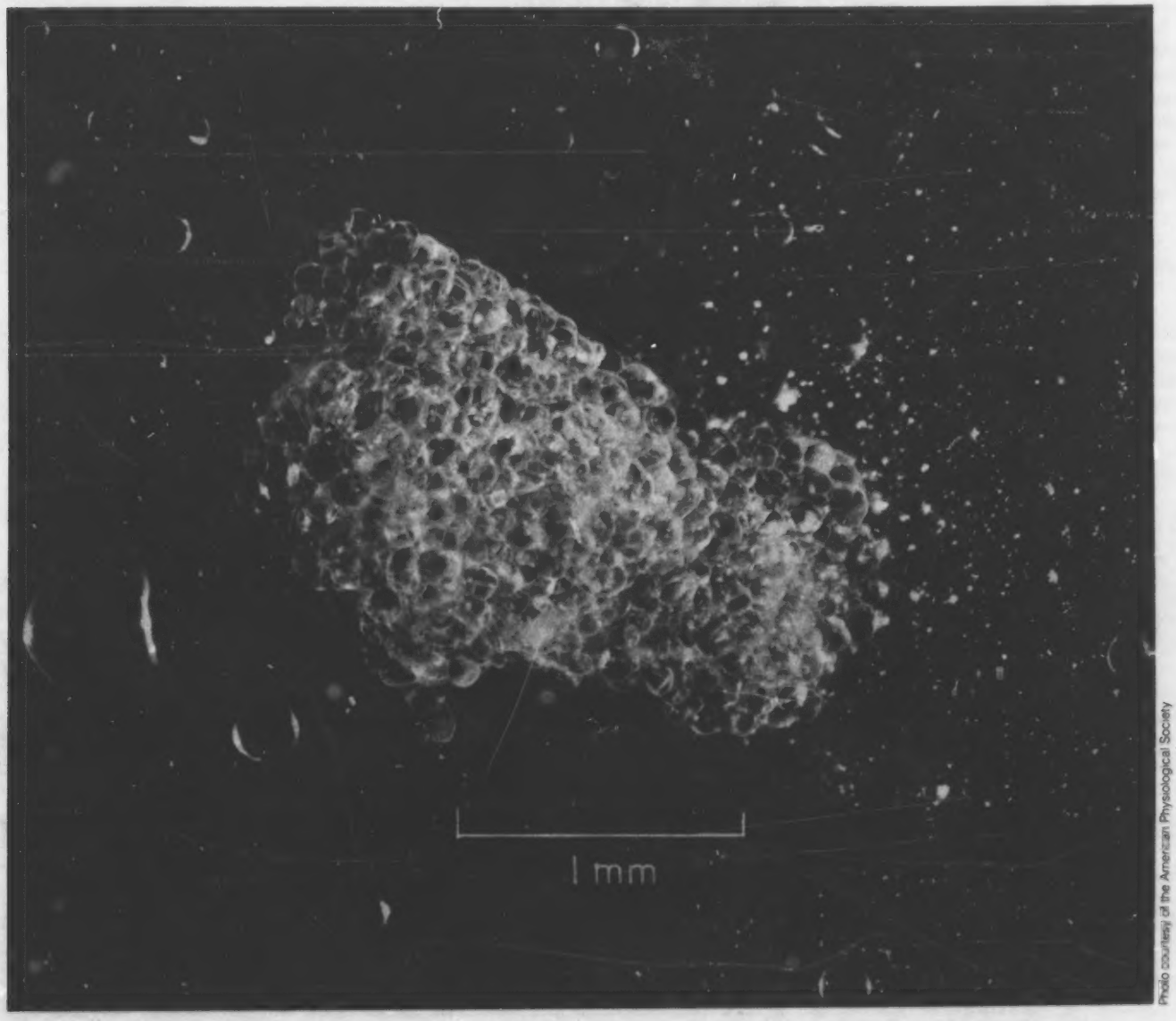


Photo courtesy of the American Physiological Society

Here is a fragment of human fat tissue surrounded by oil droplets. Researchers at the Medical College of Wisconsin GCRC in Milwaukee have correlated patterns of body fat in women with their ratio of male-to-female sex hormones and their risk for diabetes.

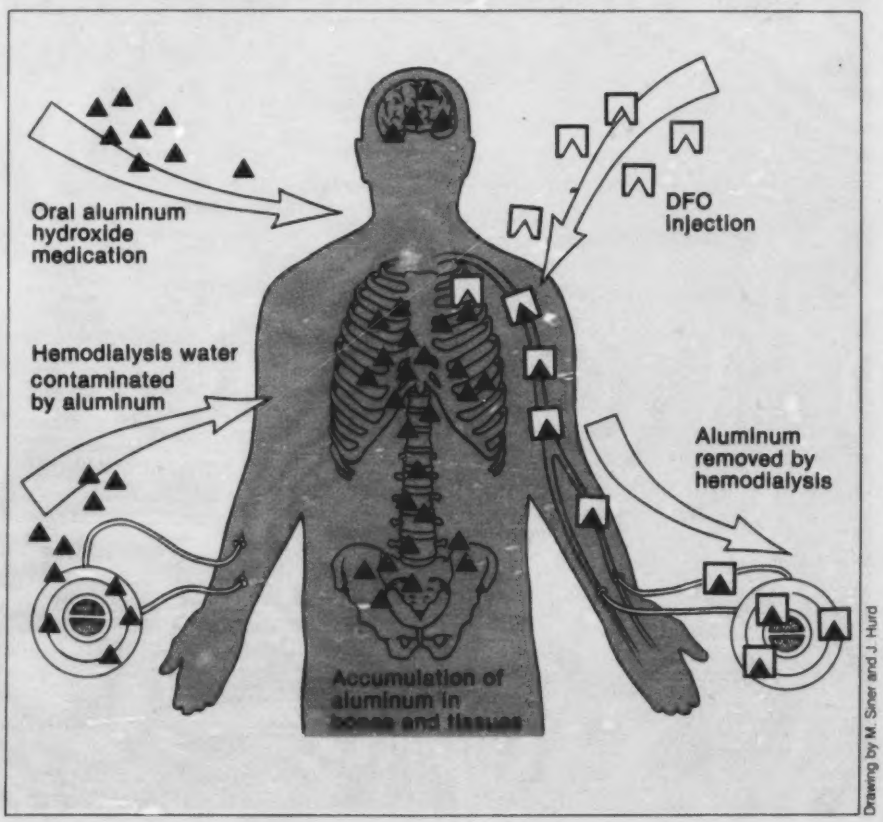
Photo courtesy of University of Minnesota Hospitals in Minneapolis

Surgeons at a midwestern GCRC reroute the bowel of a diabetic patient in preparation for a pancreas transplant that may restore the man's natural insulin supply. Diabetes research is conducted at many of the 75 GCRC's nationwide.

tissue from an identical twin. But the surgeon found that in three of the four patients the transplanted tissue stopped producing insulin a few months after the implant. Biopsies of grafted tissue showed that the patients' lymphocytes were concentrated in these pancreatic cells; the GCRC researchers believe that in the three patients the immune system was triggered to react against the transplanted cells. This type of reaction, they believed, may have replicated the shutdown of the patients' own insulin-producing cells at the onset of diabetes more than 15 years earlier. The fourth patient, who was treated with an immunosuppressive drug after the transplant, still has a functioning graft that produces insulin. The patient may need to have immunosuppressive drug therapy throughout her life in order to continue producing insulin.

Complications of Diabetes Reversed with Insulin Infusion Pump. Some of the early complications of diabetes may be reversed by treating patients with an insulin infusion pump, according to researchers at the GCRC of the University of Texas. In a study of 13 patients undergoing insulin pump therapy, thickening of some capillary basement membranes in skeletal muscle was reversed. The thickening is a side effect of diabetes. A similar thickening of basement membranes in the eyes and kidneys of diabetics, one of the disease's most serious complications, is known to damage these organs. The investigators did not directly sample the membranes in the eyes and kidneys to detect if a similar membrane thinning occurred, because such examination would injure the organs. But the researchers believe that the thinning in muscle tissue is an indication that diabetes-associated damage to eyes and kidneys also may be controlled or reversed with insulin infusion treatment.

Sex Hormone Imbalance in Women Determines Risk for Diabetes. Subtle differences in the ratio of male-to-female sex hormones may explain why women who gain weight above the waist are at higher risk for developing diabetes, according to researchers at the Medical College of Wisconsin GCRC in Milwaukee. In a group of 80 premenopausal women the investigators found that even slightly elevated ratios of the sex hormones in the blood were linked to the deposit of enlarged fat cells above the waist and to insulin resistance, a condition that often precedes diabetes. While overweight men have a higher risk than women for diabetes, there are more women than men in the United States who are obese and more women are diabetic. The study is a followup to another study at the GCRC that found that women who have excess weight in their upper body, rather than in their hips, thighs, and buttocks, may be more susceptible to diabetes. The


Oral aluminum hydroxide medication
DFO injection
Hemodialysis water contaminated by aluminum
Aluminum removed by hemodialysis
Accumulation of aluminum in bones and tissues

Drawing by M. Siner and J. Hurd

Hemodialysis patients are highly susceptible to aluminum poisoning because neither dialysis nor their defective kidneys can effectively remove the excess aluminum from their blood. Researchers, including investigators at the GCRC of the University of California-Los Angeles, have found that the binding compound desferrioxamine (DFO) can transfer aluminum from the tissues to the bloodstream. In the bloodstream the bonded aluminum and DFO can be removed easily by dialysis.

sex hormones may be an underlying cause of the link between fat distribution and diabetes. Women with lower ratios of male-to-female sex hormones had normal-sized fat cells, deposited mostly below the waist, and were at less risk of developing insulin resistance. The researchers are continuing their work to determine whether the higher sex hormone ratios alone or in concert with enlarged fat cells promote glucose intolerance and insulin resistance. The GCRC investigators recommend that women with upper body fat or a sex hormone abnormality should be alerted to a possible risk for developing late-onset diabetes.

Genetic Diseases

Genetic Marker for Autoimmune Diseases. Researchers have identified a dominant genetic factor that appears to enhance a person's predisposition to autoimmune diseases and serological abnormalities. A GCRC study at the Johns Hopkins University School of Medicine in Baltimore detected such a factor in 10 families of patients with autoimmune hemolytic anemia (AIHA), immune thrombocytopenic purpura (ITP), and systemic lupus erythematosus (SLE). High concentrations of antinuclear antibodies and antibodies to single-stranded DNA were found in a third of the relatives of two patients; one patient had AIHA, the other had ITP. Other autoimmune disorders, including rheumatoid arthritis, scleroderma, discoid lupus, and hyperthyroidism, were also detected in 21 percent of the relatives, but no disorders or antibodies were detected in the spouses. The same immunologic abnormalities were found in family members of a patient with SLE. Research has demonstrated that antibodies to single-stranded DNA appear to be a sensitive marker for immune-mediated diseases, and elevated levels of antinuclear antibodies have been found in a number of patients with autoimmune diseases. The GCRC investigators believe that the presence of both these antibody types reflects a single genetic trait in family members of the patients, probably a mendelian dominant factor. What appears to be inherited, the investigators hypothesize, is a factor that impairs regulation of the immune system and allows the body to produce antibodies against itself. The research may detect possible genetic factors in families of other patients with an autoimmune disease.

Clomiphene and Sickle Cell Anemia. The association between sickle cell anemia and delayed sexual maturation has long been recognized, but its underlying causes are not well understood. A drug called clomiphene citrate can successfully treat sickle cell anemia patients whose growth and sexual maturation have been delayed, according to scientists who conducted a study at the GCRC of the University of California in San Francisco. The sexual immaturity of the two 19-year-old sickle cell anemia patients in their study was caused by a hypothalamic dysfunction, the investigators say. The dysfunction causes a defect in the synthesis, release, or transport of a hormone called gonadotropin-releasing hormone (GnRH). GnRH normally influences the pituitary to release hormones that induce puberty. Clomiphene acts to stimulate production of GnRH, bringing the hormonal system back into balance. Treatment with the drug improved gonadal function and induced sexual maturation in the two patients.

Genetic Markers for Neurologic Diseases. Investigators at the Duke University GCRC in

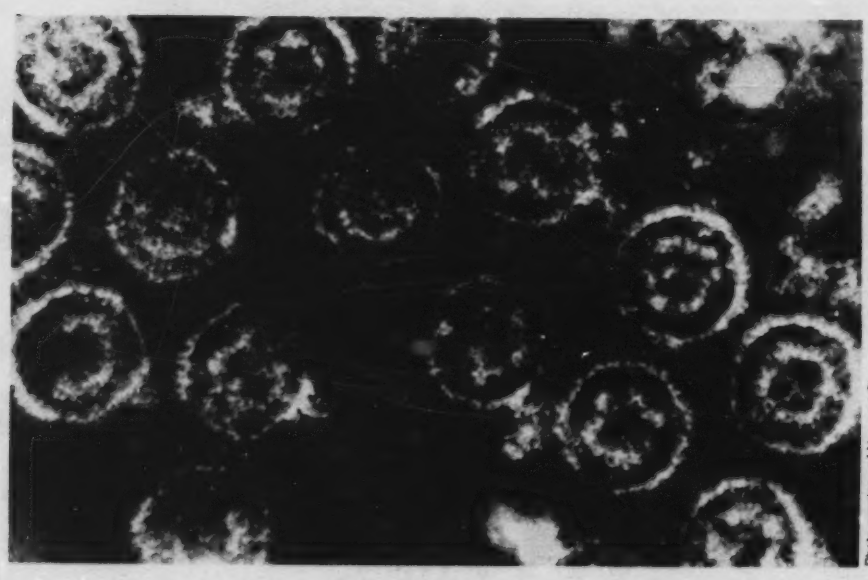


Photo courtesy of Newport Pharmaceuticals International, Inc

Shown here are samples of a genital herpes simplex virus. Research conducted at a California GCRC indicates that the virus induces in infected women the production of antibodies that may protect their newborn from the disease.

Durham, North Carolina, and other researchers are using several new genetic markers to develop a screening test for myotonic muscular dystrophy (DM). With the new markers, called restriction fragment polymorphisms, and information gathered from extensive family genetics studies, the scientists are zeroing in on the gene responsible for the slowly progressive and eventually debilitating muscle disorder. The GCRC research team hopes to develop an accurate method for determining who is at risk for DM, which may not manifest itself until late adulthood.

Immune System

Rheumatoid Arthritis Linked to Impaired Response to Herpes Epstein-Barr Virus. Earlier work at the GCRC of the Scripps Clinic and Research Foundation in La Jolla, California, showed that most patients who develop rheumatoid arthritis have responded abnormally to infection with Epstein-Barr virus. Now researchers have found that white blood cells known as T lymphocytes are much less effective in halting the spread of virus-infected lymphocytes than in patients who do not have arthritis. The T cell lymphocytes in some of these arthritic patients apparently produce less interferon, a natural antiviral agent. The interferon deficiency, in turn, has been traced to a lack of interleukin-2, a substance necessary for the differentiation of T cells. The research suggests that clinical trials of interferon or interleukin-2 might be attempted in patients with early rheumatoid arthritis.
Herpes Treatment Tested. Researchers at the University of Washington GCRC in Seattle have found that the antiviral agent acyclovir, administered intravenously, markedly decreases the lesions, severity of symptoms, and complications of primary genital herpes infection. In a study conducted at the Seattle GCRC, acyclovir shortened the duration of viral shedding from genital lesions by 85 to 90 percent, reducing the pain and symptoms associated with primary genital herpes, the most severe form of herpes infection. Treatment with the drug increased their remission periods from an average of 55 days to 126. The researchers recommend that a larger population of patients be studied to determine if intravenous administration of the drug can alter the natural course of the disease, in addition to controlling symptoms. Acyclovir is also available in a topical form, and a pill form is being developed as well. The researchers predict that the acyclovir pill will become the common choice for initial treatment of genital herpes, but they advocate intravenous treatment for the most severe cases.

Once thought too frail to tolerate vigorous medical treatment, premature newborns are surviving in increasing numbers. Increased survival is due largely to new technologies and procedures, many of which have been developed at General Clinical Research Centers.

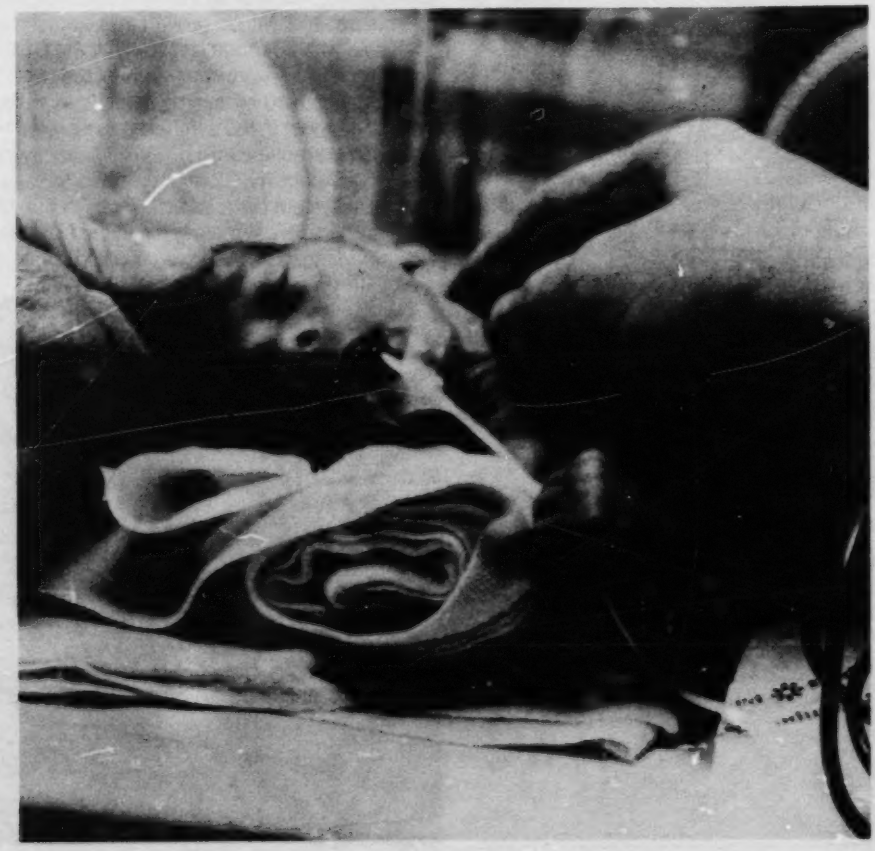


Photo courtesy of Dr. LeRoy J. Dierker, Jr., Cleveland Metropolitan General Hospital

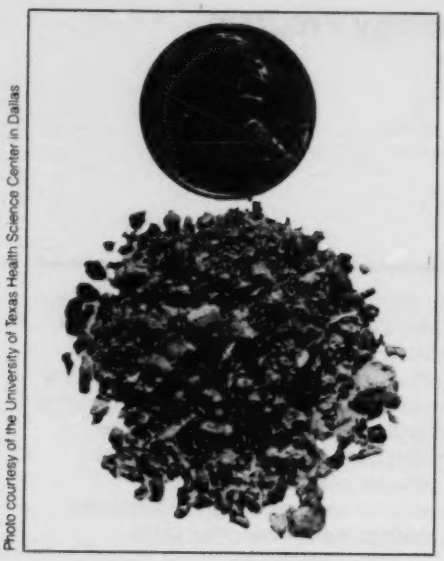


Photo courtesy of the University of Texas Health Science Center in Dallas

Despite their relatively small size, kidney stones can block the flow of urine from kidney to bladder and cause excruciating pain. Research at the GCRC of the University of Texas Health Science Center in Dallas indicates that a chemical found in citrus fruits, potassium citrate, may sharply reduce the formation of stones in patients who have the most common type of kidney stone disease.

Maternal and Child Health

Infertility Reversed in Women. Scientists have reversed infertility in some women by treatment with gonadotropin-releasing hormone, infused through a portable pump. In a GCRC study at the University of California in San Diego, all of eight women who were infertile due to hypothalamic abnormalities began to ovulate and five became pregnant. Three of the women delivered healthy babies. The women had failed to ovulate or menstruate because the hypothalamus, a brain center that controls hormonal activity, was not adequately stimulating the pituitary gland with GnRH. The infusion pump in the study replaced the hypothalamus in stimulating the pituitary gland with GnRH, which triggers the pituitary to secrete hormones that initiate and maintain the fertility cycle. The idea for pulsed infusion of GnRH has been known since 1972; its development was facilitated by animal research at the DRR-supported Oregon Regional Primate Research Center in Beaverton. Researchers at the GCRC believe the infusion technique will be widely available within the next 1-2 years, but stress that the therapy should only be used under the supervision of a physician or expert in reproductive biology.

Protection against Herpes Simplex Virus. Many investigators have noticed that many infants exposed to herpes simplex virus during birth show no symptoms of the disease. Now researchers at the Stanford University GCRC in California have found evidence that expectant mothers who have built up resistance to herpes simplex virus through recurrent infection can transfer that resistance to their fetus. In a GCRC study, antibody resistance to herpes simplex virus was detected at levels comparable to maternal resistance in amniotic fluid of mothers currently infected with HSV. According to the researchers, the findings indicate that the fetus received immune protection from its mother in the form of immunoglobulin G antibodies. Antibody activity was not found in amniotic fluid from infected mothers whose resistance to herpes was weak. Mothers who have recurrent herpes infections apparently acquire a stronger resistance to the disease, and their infants have a lower infection rate, according to the researchers. Forty-one women in the study who had genital HSV but no lesions delivered their babies vaginally without infection. All but one of the infants shared their mother's high resistance to the infection. Newborns who do contract herpes simplex virus must be treated quickly to prevent or limit injury; antiviral drugs are administered to the infant, but the infection may still cause permanent side effects or death.

Consequences of Reye Syndrome. Reye syndrome (RS) is an acute disease, often fatal, that can cause swelling of the brain, hypoglycemia, intense intracranial pressure, and damage to mitochondria in the brain and liver. The disease can strike young children as well as adults, and there is no specific treatment for the illness, other than supportive therapy. Most patients who survive RS can expect complete recovery, but some patients develop neurological problems or minor intellectual impairment. GCRC researchers at Yale University in New Haven, Connecticut, have found, however, that these problems, which seem to occur most often in people who had a severe case of the disease or were afflicted at an early age, can be temporary and often disappear with intensive therapy. In a GCRC study, investigators compared RS survivors, most of whom had been severely ill, with their siblings who never had the disease. Eight of the 16 young RS survivors showed minor neurological abnormalities, such as drooling, tics, and temporary inability to carry out familiar movements, and 11 had short attention spans. Their siblings had none of these deficits. By the end of the 3-year study, the neurological problems had disappeared and IQ measurements among the RS survivors were not significantly lower than their siblings, except for those children who had RS at a very early age. According to the GCRC researchers, results of their study indicate that children who had early disease onset or who experienced severe RS should be examined frequently after recovery.

Biomedical Research Technology Program

Program Description

The Biomedical Research Technology (BRT) Program, formerly called the Biotechnology Resources Program, was established in 1962 after Congress expressed interest in the creation of an NIH activity focused on the special technology needed for biomedical research. Since that time the Program has modified and expanded its scope. In its early years the Program mainly supported large general-purpose computer centers in medical schools. It later moved into an extremely broad and innovative array of biomedical technologies. The Program now places greater emphasis on regional and national sharing of resources. Each resource site also provides collaborative research opportunities, training, an information center, and other services. Program-supported workshops and program exhibits at scientific meetings alert researchers to the availability of these resources.

Research at the 47 resource centers supported by the Program in 1984 focused on the application of the physical sciences, mathematics, and engineering to biology and medicine. The centers are divided into four main categories: biochemical materials resources, biological and function resources, biomedical engineering resources, and computer resources. In addition to large-scale and minicomputer systems, these resources include such instruments as mass, nuclear magnetic, and electron spin resonance spectrometers; million-volt electron microscopes; lasers; flow cytometers; and vibrating probes. Some centers also produce biochemical research materials.

The complex computer systems are used primarily for statistical data reduction, mathematical analyses, biomedical modeling, and organized knowledge systems. Other computers are used for specialized operations such as monitoring vital signs in critically ill patients. The biomedical and biophysical instruments facilitate research on biological structure and function at the molecular level. The biomedical materials resources produce labeled chemical compounds for use in research.

According to the latest available statistics, 3,146 biomedical scientists working on more than 2,199 research projects used the biomedical research technology resources in 1983; more than 728 of these projects were supported by grants from 12 NIH institutes and other Public Health Service agencies. Support for other projects came from the National Science Foundation, the Department of Energy, the Department of Defense, the Federal Drug Administration, and the National Bureau of Standards.

In addition to existing grants and contracts, the program in 1984 awarded 4 new resource grants, 12 supplements to resource grants to enhance training activities, 1 resource cooperative agreement, 4 resource-related research project grants, 7 small business innovation grants totaling $290,000, and 22 small grants totaling approximately $450,000.

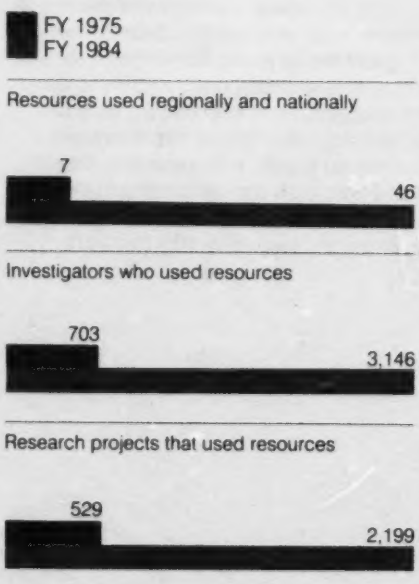
Among the new grants were three awards for nuclear magnetic resonance (NMR) resources. At the University of Pennsylvania, research will focus on probe and coil design for NMR in vivo studies; experiments will correlate energy and substrate metabolism to disease states.

A resource on NMR imaging and in vivo spectroscopy was established at the University of Florida in Gainesville; the center will emphasize collaborative studies on human and animal metabolism. The resource will also provide advice to extramural researchers and support imaging studies conducted on an existing system at the university.

A grant at the University of California in San Francisco will help scientists explore the usefulness of two-dimensional Fourier transform NMR in identifying protein structure. A new algorithm developed at the university helps to elucidate spatial and geometrical information on proteins from spectral data.

Three new awards in 1984 helped support sequence analysis and molecular structure research. A resource cooperative agreement with IntelliGenetics, Inc., in Palo Alto, California, will provide an online computer network for nucleic acid data bases and analysis programs. The goal is to foster a group of scientists with common interests who plan experiments and develop software through contact with the network.

Use of Biomedical Research Technology Resources in FY 1984 Compared with FY 1975



Another award established a Protein Identification Resource at Georgetown University's National Biomedical Foundation in Washington, D.C. The resource includes the foundation's protein sequence data base and several nucleic acid data bases. It will provide online searching and sequence analysis techniques to help identify proteins. It will also attempt to develop a computer system to predict the medical significance of proteins, based on amino acid sequences.

Funding at the University of Georgia, Athens, will promote work on molecular mechanics, a computer technique for accurately predicting molecular structures and energies. This new work will be available to scientists through the PROPHET computer resource and the Quantum Chemistry Program Exchange.

There were several new grants in 1984 for spectroscopy studies—probing the structures of proteins and trace elements and analyzing cell function. A new resource at Brookhaven National Laboratory in Upton, New York, uses a source of intense, tunable, X rays to detect minute concentrations of trace elements. The Brookhaven resource can identify elements at levels of three parts per billion in a specimen only five microns in diameter.

A new research project grant awarded to the New York State Department of Health in Albany is enabling investigators to develop three-dimensional computer simulations of projection images from the high-voltage electron microscope. Micrographs of thick sections from a tilt series will be digitized and reconstructed by computer using a modified back projection algorithm.

In addition, training grants to teach scientists methods of mass spectroscopy, synchrotron x-ray absorption spectroscopy, Fourier transform infrared spectroscopy, and electron spin resonance techniques were awarded to universities across the country.

Among seven small business grants awarded in 1984 were those for furthering the development of: silicon avalanche photodiodes, used in positron emission tomographic studies; an inexpensive method to enable computers to optically read data from clinical records; a tongue-controlled instrument to allow some paraplegics and quadriplegics to operate a computer and control other devices; and specialized multiple detectors for liquid chromatography systems.

Twenty-two small grants during the past fiscal year supported, among other projects, a feasibility study of electron spin resonance (ESR) and in vivo ESR spectroscopy;

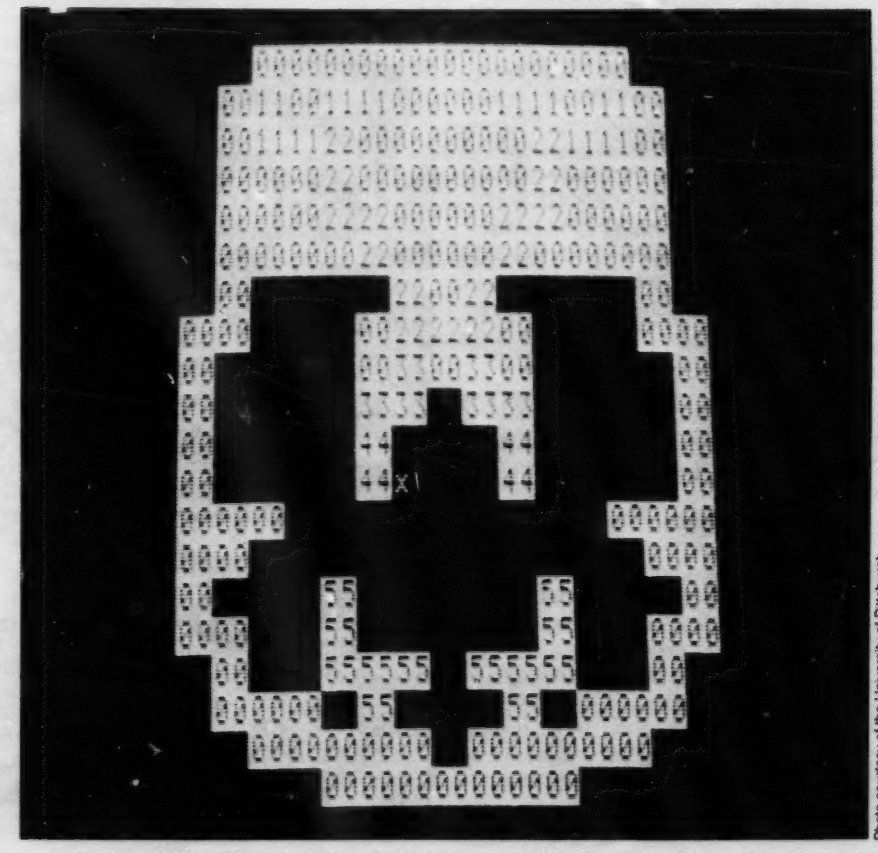


Photo courtesy of the University of Pittsburgh

A recent addition to CADUCEUS, a computer project at the University of Pittsburgh that diagnoses diseases of internal medicine, helps identify neurological disorders by dividing parts of the human body into numbered cubes. Each cube correlates with information stored in the computer about the function of the nervous system in that location; for example, 0 = skull, 1 = retina, 2 = optic nerves, 3 = optic tracts, 4 = lateral geniculate, and 5 = geniculocalcarine tracts.

investigation of sapphire as an alternative to diamond in cutting tissue for electron microscopy; and examination of the influence of radiofrequency radiation on protein separation during high-pressure liquid chromatography.

Program Highlights

Computer Resources

Computer resources supported by the BRT Program include large-scale, minicomputer, and microcomputer systems. The advanced computing, information-processing, and knowledge-based capabilities of these systems provide new insights into health problems. They also apply artificial intelligence programs to clinical decision-making, interpret molecular structures, and image cells and organs in three dimensions.

Expert Consulting Systems. Researchers at the University of Pittsburgh have developed a computer program that uses fundamental neuroanatomy to interpret patient data about the nervous system. The program, known as LOCALIZE, locates peripheral nervous system lesions that may lead to muscle weakness. With information obtained from clinical observations and use of the electromyograph, which records muscle response to electrical stimulation, LOCALIZE quickly identifies sites of single or multiple lesions that cause neurological abnormalities.

The program can explain its decisions, detect inaccurate patient data, and request information. LOCALIZE was designed as an adjunct program to CADUCEUS (formerly called INTERNIST), a large computer program at the University of Pittsburgh that gives expert advice on complex diagnoses in internal medicine. CADUCEUS is part of the SUMEX-AIM (Stanford University Medical Experimental Computer for Artificial Intelligence in Medicine) resource, a national computer network devoted to the use of artificial intelligence (AI) in medicine.

Another CADUCEUS project is a computer program that helps locate disorders of the central nervous system. A graphics program reminiscent of a Rubik's cube divides the body into hundreds of nested cubes. The largest cube envelops a computer model of the entire body. A knowledge base linked to the graphics program identifies the blood flow and neurological function of each of the smallest cubes, which measure 3 millimeters on a side. Given a set of signs and symptoms of a neurological disorder, the computer can generate a list of anatomical structures associated with the problem.

The offspring of computer resources supported by the Biomedical Research Technology Program (BRTP) are assisting physicians in diagnosing lung disorders and suggesting therapies for some cancer patients. Still evolving are BRTP-funded artificial intelligence programs to help diagnose more than 750 diseases of internal medicine and hundreds more in ophthalmology, rheumatology, and clinical pathology.

Illustration by Dan Sherbo

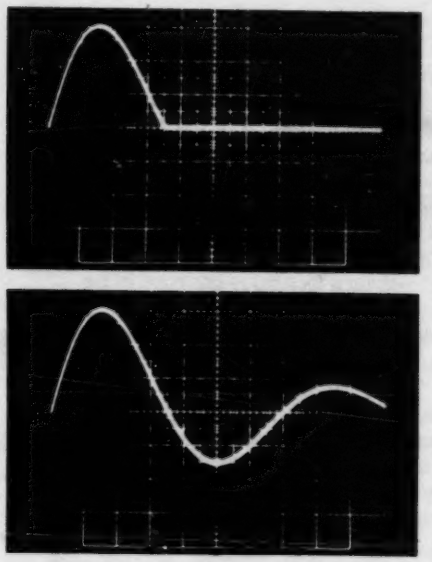


Illustration courtesy of Dr. Janice L. Jones

Modifying the standard voltage pulse for defibrillating the heart (top) by adding a "negative tail" (bottom) promises to reduce damage to heart cells and decrease postshock arrest time.

The cube approach may have application to internal medicine and to the computer interpretation of three-dimensional X ray or other medical imaging procedures. But, the researchers say, the cube model may be most important in neurology, where rapidly identifying the location of a disorder may be as crucial to saving lives as finding the exact cause of the problem.

A recent spinoff from the Rutgers Research Resource on Computers in Biomedicine is a small-scale AI program, contained on a single microchip, that offers specialized medical advice to about 200 clinics and hospitals in the United States. The microchip fits inside a scanning densitometer that detects patterns of serum proteins in a patient's blood sample. The chip interprets the patterns and assists the doctor in diagnosing blood infections and other abnormalities. Another consultation program that evolved from EXPERT runs on a hand-held computer. The program, which recommends treatment for eye disorders, is intended for use in third world and underdeveloped countries where physicians are scarce. According to researchers, the program aids paramedics in determining if patients require treatment at a medical center or if problems can be resolved onsite.

NMR Analysis Software Package. Syracuse University researchers at a resource in New York City have developed and are distributing data analysis software packages for NMR that are compatible with many computers. One of the programs, known as NMR1, helps optimize NMR spectra characterized by poor line shapes, rough baselines, and limited signal strength. This program processes one-dimensional spectra and is in use at more than 30 research centers worldwide. Another software package, NMR2, soon to be distributed to test sites, handles two-dimensional Fourier transform data. On computers with a 32-bit memory the package will allow processing of very large matrices, with up to 32 million floating point data elements.

Molecular Mechanics Computing Machine. A special digital computing system designed at Columbia University is now being built in collaboration with the Brookhaven National Laboratory. The system will analyze the interaction of proteins with other small or large molecules and compute energy minimization dynamics with a power equal to that of a CRAY-1S supercomputer. The system, called FASTRUN, and its array processor, MMCM (molecular mechanics computing machine), will be part of the Columbia University resource and will be available to users through network connections.

Improving CT Scan Images of the Heart. A computer resource at the Mayo Clinic in Rochester, Minnesota, has developed a program that enhances CT (computed tomography) x-ray scanner images of the beating heart and other moving organs. The program uses scanning geometry and the timing of successive x-ray images to produce high resolution pictures sharper than those obtained from data from a single scanner image. The algorithm is readily adaptable to current CT scanners and should improve image quality of all moving organs without increasing x-ray exposure. The sharp images produced in short-time intervals allow the structure and function of moving organs to be measured accurately.

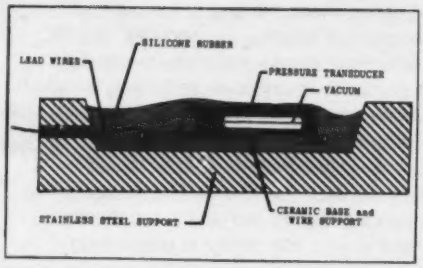
Program for Visualizing Molecules. The staff of a resource for graphics studies of molecules at the University of North Carolina in Chapel Hill has devised a computer program for visualizing molecular structure, focusing on the enzyme superoxide dismutase. Their studies are described in a 17-minute videotape entitled "What Does a Protein Look Like?," which includes 40 images of the enzyme, and by a companion paper, "Views of Unseen Worlds."

Biomedical Engineering and Digital Technology Resources

These resources engineer biocompatible devices that measure chemical and physical events in vivo and provide therapy. Computer technology to solve clinical and biomedical research problems is also developed at these facilities.

Improving Defibrillation of the Heart. More than 45 percent of heart patients who receive emergency defibrillation die, according to 1980 statistics. The survival rate of these patients may be improved if a short negative voltage pulse follows the positive pulse applied to jolt a fibrillating heart back to normal rhythm, according to researchers at Case Western Reserve University and the Case Institute of Technology in Cleveland, Ohio. Many patients who receive only the positive pulse, the standard treatment, are initially revived but later succumb to heart malfunction. Many others who do survive have ventricular arrhythmias, necrosis of heart tissue, or other cardiac problems.

One reason for these problems is that heart tissue is damaged by the same electrical pulse that earlier saved the life of the patient. The electrical pulse can depolarize heart cells, cause a breakdown of cell membranes, and prolong ion exchange. Working with heart cells from chickens, which respond to electrical shock as human heart cells do,



A pressure transducer (cross sectional view) developed at the Case Western Reserve University in Cleveland, Ohio, can assess pressure in the urethra or bladder to guide treatment of women who may have urinary leakage. The Case Western biomedical engineering and digital resource is supported by the BRTP.

investigators have found that a second, negative pulse following immediately after the positive pulse helps seal heart membranes.

In tests conducted in vitro the biphasic waveform reduced postshock arrest time and the severity of myocardial cell depolarization. The waveforms are being tested in animals before they are applied in humans to ensure that other influences on the intact and integrated heart do not interfere with beneficial effects. The next step is testing the procedure on humans, the researchers say.

Synthetic Vascular Grafts Using Electron Spectroscopy. A new treatment for altering the surface of the blood-contact-lining of artificial vascular grafts has been developed at the University of Washington Electron Spectroscopy and Surface Analysis Resource; an ultra-thin, Teflon-like coating is applied to the lining by a technique common in the microprocessor industry. The coating will greatly increase the ability of vascular grafts to resist blockage by blood clots. Because the coating is so thin, few techniques other than electron spectroscopy can determine if the surface is appropriately thin and of the correct chemistry.

Biomedical Sensors Measure Body Functions. Researchers at the Case Western Reserve University in Cleveland, Ohio, have developed a variety of biomedical sensors that measure body activity. One of the devices is a miniature implantable pressure transducer that can measure pressure in the bladder, the urethra, or the pregnant uterus. The instrument is particularly useful for measurements that must be performed rapidly, such as gauging the pressure of fluid in the uterus during labor. Measuring this pressure helps monitor the activity of the fetus during labor and delivery. In practice the tiny sensor is passed into the uterus through a catheter. When placed properly, the transducer converts the fluid pressure to signals that are processed by an external electronic system. The transducer can also assess pressure in the urethra or the bladder, which helps treat women who may have urinary leakage.

A second device is a force sensor, similar in function to the transducer. Housed in a microelectronic flatpack, the sensor floats in a gel and can measure the force exerted by a paralyzed thumb after its flexor muscles have been electrically stimulated. The test demonstrates the strength of the thumb muscles and capacity of stimulated nerves.

Another device measures the physical properties of the cervix. This system uses a balloon-tipped probe that is introduced into the cervical canal during a pelvic examination. The balloon is slowly filled with sterile water; the pressure in the balloon and the volume of water infused are recorded. The resulting data, transmitted to electronic processing circuits outside the body, indicate the patient's ability to support a pregnancy.

Instruments for the Study of Biomolecular and Cellular Structure and Function

These resources include a broad range of state-of-the-art instruments for imaging organs, cells, and molecules at minute levels of structure and function. For example, noninvasive imaging technology permits investigators to measure such physiological processes as membrane exchange kinetics, blood-tissue exchanges, and cell respiration.

Mass Spectroscopy Analyzes Biological Compounds. At Colorado Health Sciences

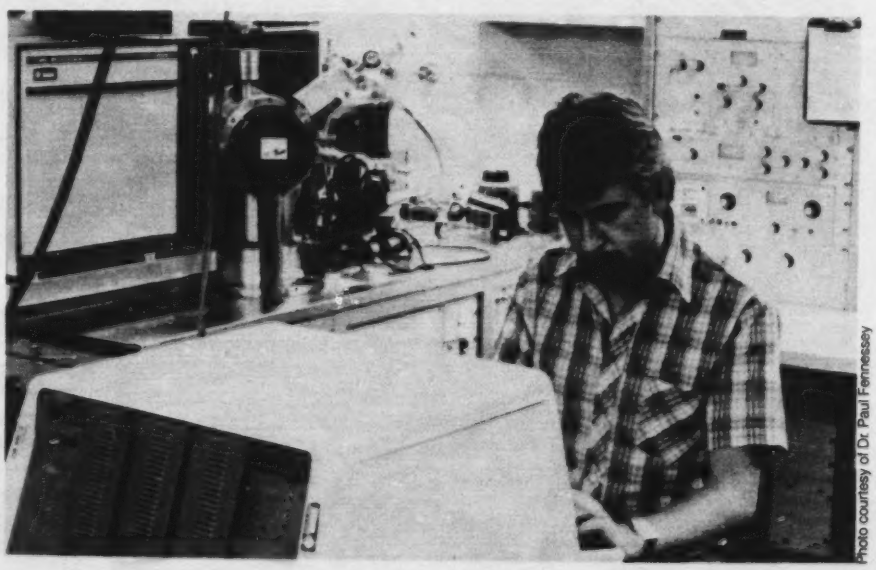


Photo courtesy of Dr. Paul Fennessey

Technicians analyze the components of biochemical compounds at the University of Colorado mass spectrometer resource. The facility is one of 47 resource centers supported nationwide by the BRTP.

University in Boulder mass spectrometers funded in part by the BRT Program are used to analyze the components of body fluids. A fast, pencil-thin beam of argon atoms is used to bombard and ionize the sample being studied, and the resulting charged species are separated according to mass in a magnetic field. The separation allows researchers to identify atomic components of substances. Investigators have used the mass spectrometers to study the kinetics of human bile acids, which aid fat absorption. They examined the effects of birth control and pregnancy on bile acid synthesis, turnover, and daily concentration. Older methods of study, which traced radiolabeled compounds in the body, posed an unacceptable health risk when performed during pregnancy. Mass spectrometry is also used at the research center to determine if a subtle chemical reaction actually occurred and to identify impurities present in known compounds.

Workshops and Conferences

Meetings supported by the BRT Program in 1984 included an international conference on the applications of mass spectroscopy to the health and life sciences, a workshop in future directions in transmission electron microscopy, a 2-week workshop at Rockefeller University in New York City on interfacing laboratory instruments with personal computers, and an international symposium on mass spectrometry. At the third international EXAFS (extended x-ray absorption fine structure) Conference at Stanford University, the applications of EXAFS to all materials were discussed, in addition to general theory, instrumentation, and use in energy loss spectroscopy. The uses of infrared spectroscopy and x-ray photoelectron spectroscopy in the biological sciences were emphasized at the fourth international meeting on new spectroscopic methods for biomedical research. Presentations at the twelfth annual PROPHET users' colloquium highlighted PROPHET research on cataracts, corticosteroids, and the design of mutagenic modifications of alpha-globulin with the aid of molecular graphics. A task-force meeting to review the status of high-mass spectroscopy was also held.

Future Directions

Plans for the future of the PROPHET computer resource were developed during the year. An advisory panel was formed to provide advice on the future directions of the computer system; as a result of the panel's recommendations a request for proposal to redevelop the system was issued. A Prophet User Committee, called OPUS, was also organized; the BRT Program staff will meet with the group several times a year to discuss future needs for the system. OPUS will also assist in the organization of the annual PROPHET colloquium; a newsletter called the OPUSLETTER was established to inform PROPHET users about the group's activities. The software redesign, testing, and documentation of the second generation of PROPHET, known as PROPHET II, is scheduled to be completed within 3 years. The system, which will feature a distributed network, is expected to be in general use after an additional 2 years.

The BRT Program is exploring the potential of new developments in mass spectroscopy for analyzing compounds with molecular weight up to 10,000 daltons. The use of heavy ions in the mass spectrometer may allow study of large molecules, such as peptides that are potent regulators of the endocrine and nervous systems, as well as carbohydrates that figure in cell recognition, transformation, and development. Fast characterization of synthetic nucleotides is also possible.

The BRT Program will consider funding several new in vivo NMR resources in Fiscal Year 1985. The NMR resources will aid studies of physiological metabolism in healthy and diseased tissues, the central nervous system, and energy balance in various organs. The program also will consider establishing new intermediate voltage electron microscopy (IVEM) facilities. The IVEM's are expected to bridge the gap between conventional electron microscopes and high-voltage machines, potentially saving costs by obtaining results at 300 to 500 kilovolts which now require 1 million volts.

Also being considered for funding is access to supercomputers for biomedical scientists. Discussions were held with the National Science Foundation (NSF) about its supercomputer program, and applications of these machines to the biological sciences were examined in a December 1984 NSF workshop.

Animal Resources Program

Program Description

Animal research enables scientists to study normal physiological systems and disease processes in models, as a means to achieve better understanding of the biological systems and disease conditions of humans. The long-term study of research animals also provides information about a variety of diseases, including genetic and age-related illnesses such as arthritis, diabetes, and heart disease, that cannot yet be obtained from in vitro or human studies.

To meet these goals and fill the need for a variety of healthy animals and suitable animal research facilities, breeding environments, and other resources, DRR established the Animal Resources (AR) Program in 1962. The AR Program consists of two subprograms: the Primate Research Centers (PRC) Program, which supports seven regional primate research centers, and the Laboratory Animal Sciences Program (LASP), which supports primate breeding, specialized animal models and colonies, laboratories for the diagnosis and control of diseases of laboratory animals, and many other resource projects, including the training of specialists in animal care. Some of the breeding colonies begun by LASP have been so successful in maintaining certain species of nonhuman primates that they have been turned over to commercial developers.

Primate Research Centers Program

The NIH began the PRC Program in 1960; by 1965 seven regional primate research centers were operating. These centers provide specialized staff and environment for nonhuman primate studies and primates to model a variety of human ailments ranging from infectious diseases to developmental and behavioral problems.

Each center has a special research focus and serves as a regional and national resource. The seven centers are located in Beaverton, Oregon; Seattle, Washington; Southborough, Massachusetts; Atlanta, Georgia; Madison, Wisconsin; Covington, Louisiana; and Davis, California.

Forming the largest primate research network in the world, these centers have greatly facilitated medical advances in reproductive biology, infectious diseases, behavioral sciences, neurosciences, toxicology, nutritional and metabolic diseases, environmental health, and numerous other areas of research.

In addition to conducting basic research, the primate centers also promote scientific study nationwide by providing animal tissue specimens to outside investigators. During

Photo by Ron Cowen

Healthy rhesus monkeys in an outdoor cage at the California Regional Primate Research Center.

1984, 4,192 specimens were distributed to 379 scientists throughout the United States.

The AR Program funds administrative, operational, and resource-related costs of the centers; in 1984 this included support for 135 core staff scientists and professionals. During 1984 the program maintained 763 doctoral-level, technical, and administrative staff at the centers. In 1984 the Program provided a total of $22,361,171 in core support and $213,038 in cofunding for research at the centers. A total of 539 collaborative or affiliated investigators also conducted research at the centers, and the primate centers trained 178 graduate students engaged in thesis research.

During the past year detailed assessments of the physical conditions at the primate centers, now nearly 25 years old, were conducted. The evaluations revealed the need for extensive renovations and repairs, as well as the replacement of major equipment. The cost for these improvements is estimated at more than $13 million during the years 1984-1988. Congress allocated a special fund of $1 million during 1984 so that the centers could begin making high-priority repairs.

Laboratory Animal Sciences Program

The Laboratory Animal Sciences Program (LASP), founded by the AR Program in the mid 1960's, supports two goals: to develop animals with unique characteristics for research and to improve the health care of such animals. The LASP supports domestic breeding of nonhuman primates not available from their countries of origin, as well as studies that seek animal models of human disease. Animal model and colony projects provide scientists with animals which have known genetic predispositions toward given diseases. By breeding and observing these animals for several years, scientists can obtain information on the genetics, causes, and age-related aspects of particular diseases or disorders.

To ensure that only healthy animals are used in biomedical research, the LASP supports resource laboratories, resource-related research, and improvements of animal research facilities.

In 1984 the LASP supported 67 research or resource grants, 10 institutional training programs, and 3 individual fellowship awards for a total of $8,978,197. Researchers working at resource laboratories investigate naturally occurring diseases and laboratory-related animal problems. For example, 1984 projects included the control of a respiratory infection in rodents, development of a rapid diagnosis of herpesvirus in monkeys, and identification of risk factors in mice for infection with Sendai virus.

LASP diagnostic laboratories also investigate new laboratory animal models of human disease and produce tissue specimens, slides, and photographs for use in animal research and research training. Resource-related research projects are funded to investigate the causes, symptoms, and control of naturally occurring animal diseases that can distort research data. Improvement projects help institutions upgrade their animal facilities and develop centralized programs of animal care that comply with the Animal Welfare Act and DHHS policies on the care and treatment of animals. Funds are used to upgrade cages and sanitation equipment and for facility renovations.

Small business innovation research (SBIR) grants, in which the DHHS began to participate in 1983, are intended to stimulate technological innovations and to increase the participation of small businesses in meeting Federal research needs. The three SBIR grants funded in 1984 included projects for culturing amphibians used in biomedical research and development of a microcomputer data base for managing animal resources.

Finally, the LASP supports a variety of other animal resource projects such as the *Laboratory Primate Newsletter* and the *Registry of Comparative Pathology* located at the Armed Forces Institute of Pathology. The LASP also provides partial support for the Institute of Laboratory Animal Resources (ILAR) of the National Academy of Sciences and for the accreditation program of the American Association for Accreditation of Laboratory Animal Care. Institutional and individual training programs supported by the LASP offer veterinarians specialized training in laboratory animal medicine. This prepares them to provide professional care for laboratory animals and to conduct research in the fields of laboratory animal and comparative medicine.

Primate Research Centers Program

Administrative efforts to strengthen center programs for the care and use of primates, research progress on simian acquired immune deficiency syndrome (SAIDS), and a SAIDS workshop were among the most prominent program activities of 1984. Research findings on respiratory distress syndrome, sickle cell anemia, and other diseases were also significant. In addition to studies by core scientists, the PRC's continued to extend

Productivity Indicators of the Primate Research Centers Program in FY 1984 Compared with FY 1975

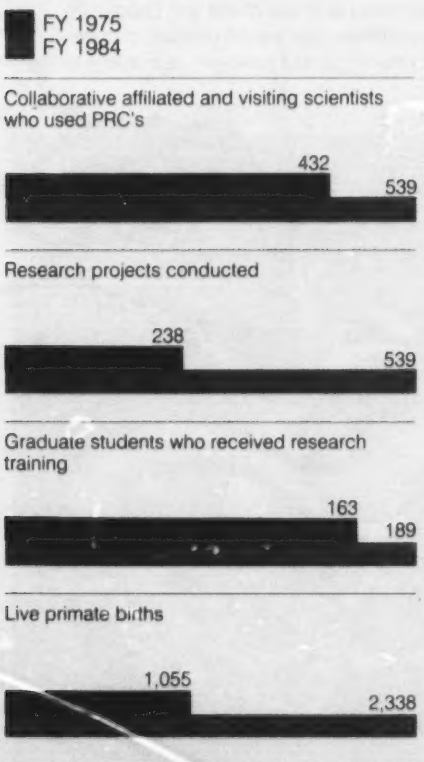


Photo courtesy of House Ear Institute

An audiologist works with a 2-year-old child who received a cochlear prosthesis. Animal studies at the Washington Regional Primate Research Center have helped spur development of a new type of "artificial ear."

the use of their resources to a larger group of scientists and to increase primate breeding within the centers.

Continued domestic breeding efforts at the centers resulted in 1,800 primate births, representing approximately 75 percent of the PRC's total primate requirements. The centers also maintained nuclear colonies of a number of less commonly used primate species. In all, the centers maintained approximately 13,168 primates representing 35 species, for domestic breeding and for research. The resulting research was documented by 808 journal articles, books, and book chapters, and by numerous research abstracts. Some examples of research highlights are discussed in the following paragraphs.

Rhesus Monkeys Model Human Menopause. Rhesus monkeys are providing investigators at the Wisconsin PRC in Madison with an animal model for the symptoms and biochemical changes associated with menopause in women. Because of similarities in the rhesus and the human reproductive systems, scientists believe that pinpointing the causes of hot flushes, hormonal changes, and bone deterioration in a colony of mature female monkeys may lead to more effective ways of easing the discomforts associated with menopause in women. In a rare colony of female rhesus monkeys aged 14 to 28 years—the equivalent of 30 to more than 50 years in humans—researchers plan to investigate organs and functions of the reproductive system likely to influence menopause, including the feedback mechanism involving the hypothalamus, the pituitary gland, and the ovaries. The study may give investigators clues about how menopause occurs in both monkeys and women and enable them to examine its adverse effects.

"Artificial Ear" Tested in Monkeys. Researchers at one primate center are investigating the possible health risks and benefits of the cochlear implant, an "artificial ear," that allows some deaf people to hear. The implant electrically stimulates auditory nerve fibers in the inner ear, giving the sensation of sound to deaf people who have a special type of hearing impairment. Tiny hair cells in the inner ear of these patients, which normally convert sound to electrical signals, fail to function, resulting in deafness. The implant acts as a prosthesis, bypassing the damaged tissue and allowing some deaf people to distinguish the sounds of a doorbell, a baby crying, or a traffic horn. Some human speech may also become intelligible.

One of the cochlear implants recently received FDA approval, but questions remain about the possible health risks of implanting electrodes in the ear. Basic studies in animal models at the Washington PRC are aimed at detailing the physiology of the ear and applying the knowledge to problems with the cochlear implant. For example, tests conducted in rhesus monkeys and guinea pigs at the PRC indicate that the implant may cause tissue and nerve damage to the still functioning portions of the ear. Long-term electrical stimulation of the inner ear by the implant may also cause unwanted bone growth, according to the PRC investigators. Another potential problem, according to the

A colony of aged female rhesus monkeys at the Wisconsin Regional Primate Research Center provides a model for studying the causes of hot flushes, hormonal changes, and bone deterioration associated with menopause in women.

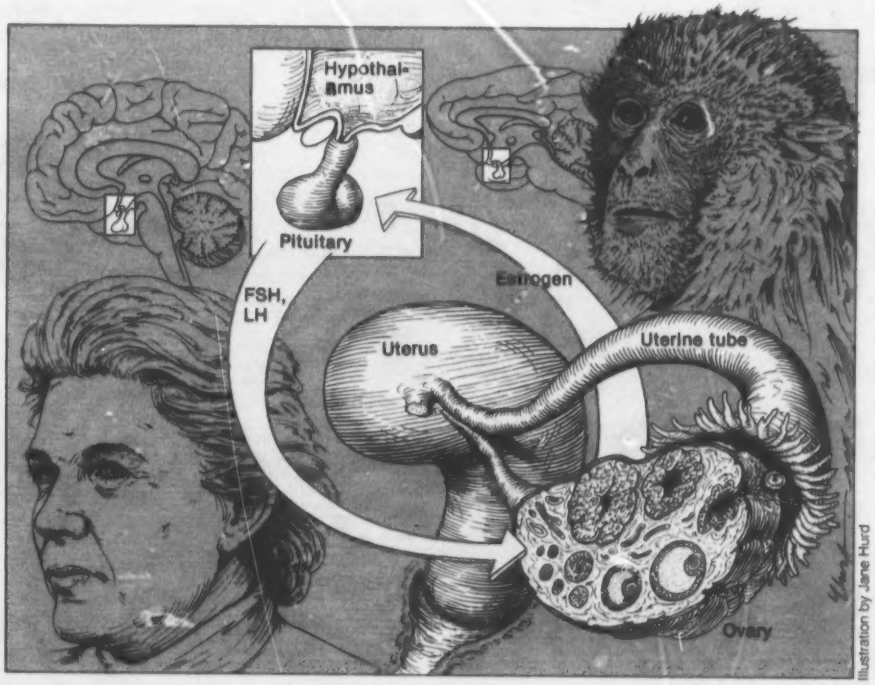
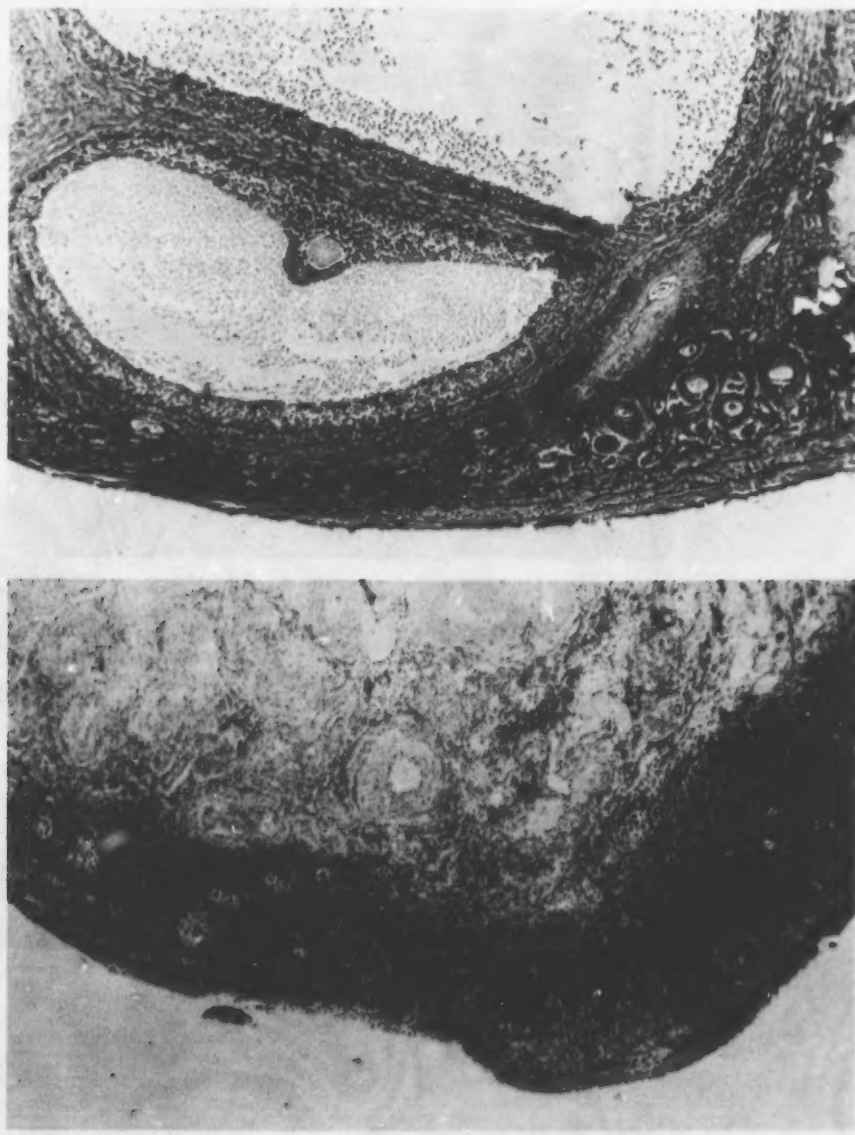


Illustration by Jane Hurd

researchers, is that infection, particularly meningitis, may spread through the surgical opening needed to insert electrodes into the cochlea.

Preliminary results at the PRC indicate that hearing impaired monkeys responded equally well to another type of electrical implant that does not require an opening in the inner ear, which reduces the risk of infection. Investigators are also studying models of the inner ear to learn more about the normal function of hair cells and how the inner ear conducts electricity. Planar and cylindrical conductors that simulate the cochlea are placed in a salt water solution that approximates the fluid in the inner ear. Electrical sources placed on or in the conductors are analyzed by computer to determine which array of electrodes in the cochlear implant produces signals that most closely follow the natural conduction paths of the ear. The PRC investigators say more long-term studies must be done to determine the lifetime effects of the implant.

Fertility of Monkeys Allows Testing of Theory of Human Birth Defects. The birth of a "test tube" rhesus monkey at the Wisconsin PRC, only the second nonhuman primate of its kind, may provide investigators with an animal model for testing a theory about the origin of certain human birth defects. The theory is that many defects occur when eggs past their prime are fertilized. By aging the eggs or sperm of rhesus monkeys and studying the development of the resulting embryos, the researchers hope to determine the correlation between birth defects and delayed fertilization. Some of the human birth defects believed to fall under this category include spina bifida, a spinal defect; microcephaly, underdevelopment of the head associated with mental retardation; and



Shown here are ovarian tissues from an 18-year-old rhesus monkey (top) and a 30-year-old rhesus monkey (bottom). Ovarian follicles (large, white areas), which are prominent in the younger rhesus, are barely visible in the older monkey. The same difference is a hallmark of human menopause.

Micrographs courtesy of Wisconsin Regional Primate Research Center

malformation of limbs. Many other defects, such as developmental abnormalities, may have the same cause, although Down syndrome, for example, has been linked to a genetic defect in the egg before ovulation.

Evidence from experiments in rodents and pigs has given support to the delayed fertilization theory, but it has been difficult to extrapolate data from these species to humans. The birth of the monkey called Petri—named for the dish in which he was conceived—is living proof, the researchers say, that a pool of such animals can be safely and accurately developed to closely test the birth defect theory. Because monkeys reach maturity about five times as rapidly as humans, defects can be detected earlier in the animals, and studies can be accelerated.

Respiratory Distress Syndrome in Premature Primates. Respiratory distress syndrome is the third leading cause of infant death in the United States. The syndrome prevents surfactant, a natural lubricant, from adequately lining the air sacs of the lungs. In both humans and monkeys with the condition, the air sacs may collapse and suffocation may occur without treatment. A team of researchers at the Wisconsin PRC is documenting healthy lung development in fetal rhesus monkeys. The hope is to identify the mechanisms that control lung development and produce surfactant. Investigators at the PRC are also studying the effects of nutrition on respiratory function and surfactant production. Another group of scientists at the Washington PRC is conducting similar research but from a different perspective. The group is monitoring and correlating a wide spectrum of factors that may influence the development of respiratory distress syndrome, including lung pressure and volume, and immunological elements present in the lung alveoli. Because basic research in both animals and humans is immediately applied to infants with the syndrome, their care is gradually improving as new information bolsters existing treatments.

Shrinking Arterial Plaque in Cynomolgus Monkeys. Animal research has recently demonstrated that atherosclerosis may be reversed with diet or drug treatment. The disorder, caused by the build up in arteries of fat, cholesterol, and other substances collectively known as plaque, can block blood flow and promote heart attacks. At the Oregon PRC cynomolgus monkeys with atherosclerosis that were treated with the drug cholestyramine or put on a low-cholesterol or alfalfa-supplemented diet had dramatic shrinkage of arterial plaque.

Researchers at the Wisconsin Regional Primate Research Center aspirate eggs from the ovarian follicles of a rhesus monkey. Ova which have aged beyond their period of optimal activity will eventually be fertilized in vitro to determine whether some birth defects are caused by delayed fertilization.

Photo by Bob Dodsworth

In the study, 72 monkeys were fed a high-fat, high-cholesterol diet for 6 months. Eight other monkeys were fed the same diet, but for only 1 month. The 72 monkeys were then divided into 3 groups: 18 monkeys were used to confirm the diagnosis of atherosclerosis, a second group of 36 continued the fatty diet, and another group of 18 were totally withdrawn from the fat-cholesterol diet. Half of the monkeys who continued the fatty diet also received alfalfa meal. After 18 months monkeys that received alfalfa meal along with the fatty diet had a decrease in arterial plaque to the level of monkeys fed the fatty diet for just 1 month. Monkeys who were withdrawn from the cholesterol-fat diet also achieved lower plaque levels, but monkeys who continued the diet without an alfalfa supplement continued to have high levels of arterial plaque. The drug cholestyramine was also found to shrink arterial plaque in the monkeys.

The researchers determined that saponins, a chemical family present in a variety of plants, including alfalfa, caused the plaque shrinkage in the monkeys fed the supplemented diet. Alfalfa itself may not be a recommended treatment for atherosclerosis in monkeys because another substance present in the meal and sprouts can cause an autoimmune disease in the animals. And although both drug and diet treatments helped decrease plaque in the monkeys, the treatments cannot stop the growth of fibrous tissue in the inner lining of arteries, the researchers say. The investigators recommend that further studies be done to determine if alfalfa or cholestyramine will shrink plaque in humans as dramatically as in the cynomolgus monkeys. An advantage of beginning with the monkey model is that accurate anatomical observations can be made and experimental diets can be rigidly controlled.

Research in Acquired Immune Deficiency Diseases. Scientists at four primate centers and the NIH have discovered viruses that may cause a monkey disease strikingly similar to acquired immune deficiency syndrome (AIDS), the chronic illness that has killed more than 3,600 people in the United States from 1979 through December 1984. Researchers are already isolating and identifying the virus or viruses associated with simian acquired immune deficiency syndrome (SAIDS) by applying the same techniques that were used to discover and characterize the closely related virus that is believed to cause human AIDS. Work on SAIDS is producing good models for research on human AIDS that promises to accelerate work already being done at NIH and elsewhere on development and testing of vaccines and drugs and clarifying important epidemiologic features of the disease.

Laboratory Animal Sciences Program

LASP-supported activities in 1984 produced a healthy group of domestically bred nonhuman primates, a variety of useful animal models and colonies, improved health care of laboratory animals, upgraded animal research facilities, and expanded research training opportunities. Recent studies that the LASP funded include: a ferret model for *Campylobacter jejuni,* an organism that causes diarrhea in humans; control of respiratory disease in rodents; development of a live vaccine to help prevent pasteurellosis in rabbits; and establishment of risk factors for Sendai virus infection in mice.

Primate Breeding. In addition to the seven Regional Primate Research Centers, the Animal Resources Program supports other nonhuman primate resources through LASP. These include one contract and four grants for the domestic breeding of nonhuman primates. The program also continued to fund an island colony of more than 680 rhesus monkeys and the Primate Supply Information Clearinghouse.

As of June 30, 1984, the contract-supported colony consisted of approximately 2,688 rhesus monkeys with 881 female breeders and 275 cynomolgus monkeys with 139 female breeders. Approximately 510 rhesus monkeys and 58 cynomolgus monkeys were sold to U.S. biomedical scientists. Because production of rhesus monkeys at commercial sources has proven feasible, phase-out of the contract was begun.

The grant-supported primate breeding projects establish production colonies and determine proper husbandry techniques for maintaining these colonies. The program continued to fund colonies of baboons, squirrel monkeys, and two species of Galagoes (bushbabies). Typical of these groups is a 4-year-old colony of squirrel monkeys, with a population of 115 females and 73 pregnancies reported in 1984. A computer-based mathematical model that predicts long-range demographic changes in the squirrel monkey colony has been introduced and promises to be a valuable tool that can be easily adapted to other breeding colonies.

LASP also supported an island colony of 680 rhesus monkeys, located at the Caribbean Primate Center of the University of Puerto Rico. Scientists use these monkeys, whose genealogical records date back to 1938, for social and behavioral studies. The colony is divided into four social groups. Primates are also housed at Sabana Seca near the University of Puerto Rico campus as subjects for pilot studies on tropical diseases, and

as models for studies of eye disease and degenerative diseases associated with aging. In addition, the National Institute of Neurological and Communicative Disorders and Stroke maintains a colony of rhesus monkeys for fetal studies at the Caribbean center.

The Primate Supply Information Clearinghouse promotes conservation and maximum research use of available primates by referring investigators who need primates, primate tissues, and related resources to the primate facilities that have these items available. During 1984 the Clearinghouse placed 7,135 living primates; arranged for the transfer of 156 cadavers, tissues, and other specimens; and filled 26 requests for primate cages and other services.

Animal Models and Special Colonies. In 1984 the LASP funded seven animal model and colony projects. These included a resource for marine invertebrate models of neurological and other biological processes; a colony of short-tailed opossums that may provide a new model for medical research; and colonies of mutant mice that model endocrine, neurological, and immunological problems.

The usefulness of the squid in neurological research—particularly its giant axon and synapse system—has been highly publicized, but locating adequate numbers of this mollusk for research has been difficult. Marine invertebrate projects are developing methods to increase the population of octopuses and loliginid squid available for neurological research. One of the projects has become a year-round source of *Lolliguncula brevis,* a small, hardy squid that is useful in studies of osmotic stress, behavior and body patterns, phototransduction, the blood-brain barrier, and nerve regeneration. Improved shipboard transport and laboratory maintenance techniques have led to the longest survival of any wild-caught loliginid squid. New technology also enabled the squid *Loligo* to be cultured throughout its life cycle for the first time, giving the resource the potential to provide all sizes of this squid to researchers.

Another colony recently developed is the short-tailed opossum, a marsupial native to Brazil. This animal has many characteristics that make it ideal for research—small size, tameness, prolific breeding in captivity, and short gestation time. These features are in marked contrast to the severe research limitations of the Virginia opossum, the North American species that is more widely available. The colony project aims to establish a suitable diet and husbandry techniques that will increase production of the short-tailed opossum. Infant opossums and other newborn marsupials are particularly good candidates for immunologic studies because they lack the natural defenses of thymic lymphoid tissue, peripheral blood lymphocytes, and immunoglobulins.

Resource Laboratories. These LASP-funded laboratories develop resources for research and training, support studies on the causes of disease in laboratory animals, and aid in the search for new animal models for human diseases. The laboratories use surveillance and monitoring techniques to discover animal health problems that, if undetected, can compromise research results. One laboratory in 1984 diagnosed Tyzzer's disease in rabbits from a commercial supplier before they were shipped to research facilities. Another resource has begun a minimal-disease rabbit colony in collaboration with a commercial rabbitry. No infectious disease has been detected in the colony, which is being expanded so that the rabbits may be routinely used in research.

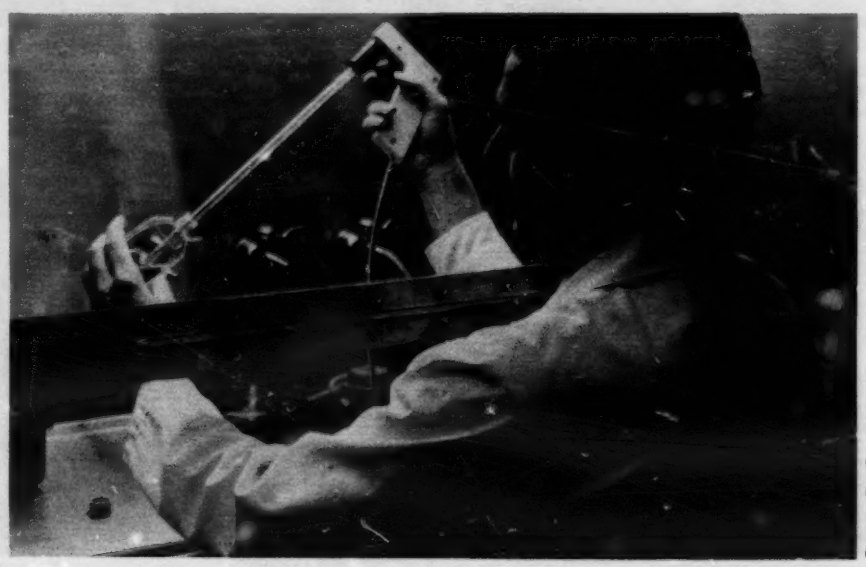


Photo by Ron Cowen

A virologist at the New England Regional Primate Research Center infects lymphoid cells with a type D retrovirus isolated from monkeys at the center that have developed simian acquired immune deficiency syndrome.

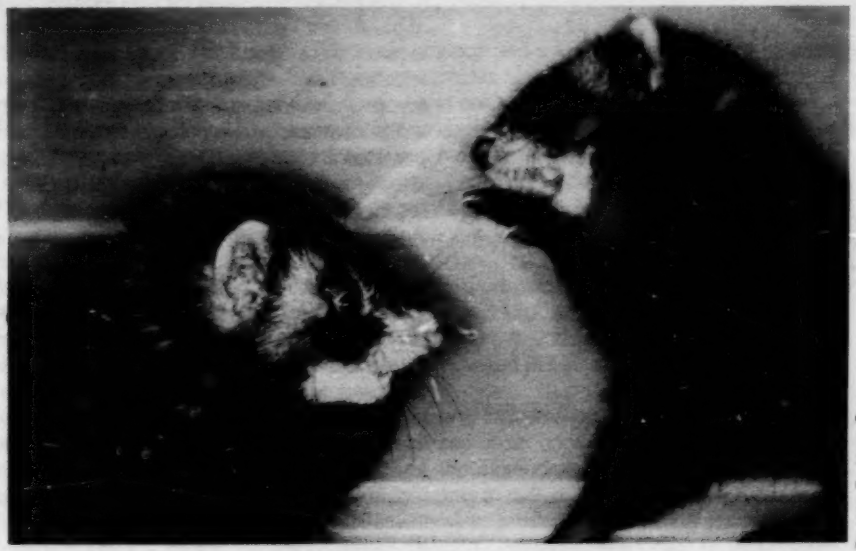


Photo by Dr. James Fox

In 1984 the Laboratory Animal Sciences Program funded seven animal model projects and animal colonies. One such project is research on the ferret, which becomes naturally infected with the bacterium C. jejuni *and develops a type of diarrhea similar to that caused in humans by the same bacterium. Researchers hope to use the ferret model to understand how* C. jejuni *causes the disease, which can be particularly debilitating in children and the elderly.*

Another center has developed a genetic monitoring program to detect abnormalities in common strains of mice and rats. Both standard isoenzyme techniques and the less common method of using strain specific antisera, a procedure previously reported in England, are used to survey the mice.

At one resource investigators collaborated to eradicate *Mycoplasma,* a common infection, from a mouse colony involved in embryo transplant research. The infection can alter the immune system in rats, according to the work of another LASP laboratory. When antibodies to *Mycoplasma* were detected in the sera of mice in the colony, researchers transplanted the embryos to disease-free mothers, which were then placed in isolation. The transplanted stock has remained free of the infection.

Also in mice, another resource has found that two particular rotavirus enzyme immunoassays are simple and sensitive diagnostic tools for detecting rotavirus infection. Rotaviruses often cause intestinal infection in newborn and young mice, causing a syndrome known as epizootic diarrhea of infant mice (EDIM). The resource determined that immunoassays using either antigens or antibodies to EDIM virus were accurate indicators of rotavirus infection.

Although long-term infection with the tapeworm *Taenia taeniaeformis,* commonly found in cats, had been known for more than 60 years to cause liver sarcoma in laboratory rats, no other *Taenia* tapeworms had been linked with cancer. But, recently, one of the LASP resources demonstrated that a second species of the *Taenia* tapeworm, as well as the *Echinococcus* tapeworm, may also cause cancer when maintained for long periods in the peritoneal cavity of rats.

Resource-Related Research. Resource-related research seeks to improve the health and availability of research animals and to gather information needed to manage animal resources effectively. In 1984 the LASP funded 19 resource-related research projects, including 6 new studies. The new projects include a study of mouse hepatitis virus in laboratory mice, evaluation of a vaccine to prevent pasteurellosis in rabbits, the response of mice to ectromelia (mousepox) virus, and methods to increase ovulation and optimize conception in dogs.

Institutional Animal Resource Improvements. During the past 14 years institutional improvement grants totaling $17.3 million have helped 125 facilities comply with the Animal Welfare Act and DHHS policy on animal welfare.

Other Animal Resource Projects. In 1984 the LASP partially supported the Institute of Laboratory Animal Resources (ILAR) of the National Academy of Sciences, the accreditation program of the American Association for Accreditation of Laboratory Animal Care, and funded several information projects and three reference centers.

The ILAR provides technical and scientific information to biomedical scientists on a variety of issues pertinent to the humane care of laboratory animals. Additional support for ILAR comes from several other government agencies.

LASP-supported information projects include the *Laboratory Primate Newsletter,* the *Registry of Avian Genetic Stocks,* and publication of a handbook on marine invertebrate development. The handbook will inform researchers about collecting adult specimens, obtaining gametes, and how to maintain a broad range of invertebrate species.

The funded reference centers include the Registry of Comparative Pathology located at the Armed Forces Institute of Pathology, and the Simian Virus Diagnostic Laboratory, located at the Southwest Foundation for Biomedical Research in San Antonio, Texas. A relatively new LASP-supported project, located at the Jackson Laboratory, is a cryopreservation bank of murine germ plasm.

The comparative pathology registry has a large collection of tissue specimens from primates and other laboratory animals, domestic and wild animals, fish, and birds. These specimens are used by scientists to prepare exhibits, lectures, and publications. The registry publishes a quarterly *Comparative Pathology Bulletin.* A handbook entitled *Animal Models of Human Disease,* covering 281 models in 12 fascicles, has been prepared for sale. In 1984 the registry continued to prepare one or two descriptions of an animal model for publication each month in *American Journal of Pathology.* The registry also continued its annual 3-day course in comparative pathology.

The Simian Virus Diagnostic Laboratory provides definitive diagnostic services on viruses that may be present in primate tissues; maintains a repository of simian viruses; and prepares reference seed viruses and specific antisera to these viruses. The laboratory also provides consultative services and encourages the exchange of information and of viral agents among primate centers and other health organizations. It trains students interested in virological laboratory procedures associated with primate research. During the last reporting period the laboratory received from a total of 49 institutions 1,393 serum specimens, 45 specimens for virus isolation, and 16 viruses for identification.

The cryopreservation reference center, now in its third year of operation, has established a bank of frozen mouse embryos to assure the preservation of mutants and strains of mice that are valuable to many fields of research. To date the bank has frozen more than 250,000 embryos from approximately 350 different strains. In many cases cryopreservation will allow reduction of the size of mouse colonies maintained by conventional breeding procedures. Because their embryos have been safely preserved, more than 40 strains of mice are no longer actively bred.

Training. In 1984 the AR Program funded nine institutional training programs, one institutional summer training program, three postdoctoral fellowships, and four research career awards in laboratory animal science and medicine. Approximately 203 trainees and fellows have completed training since the inception of the programs. Sixty-six of these are employed by medical schools and 77 by other academic, research, or governmental organizations. A majority (118) are serving as directors or staff members of vivaria; 62 are engaged in teaching and research or are obtaining additional training; and 17 are in public health, private practice, or are retired. The Special Emphasis Research Career Award (SERCA) was established in 1982. This award is intended to provide laboratory animal scientists with additional experience and time to conduct research. Four awardees, now in their second year of study, conduct research in the areas of immunology, toxicology, virology, and immunogenetics. An additional award was made in 1984 for research on a host-parasite system as a model of hypersensitivity reactions in the small intestine.

Photo by Bob Dodsworth

Pictured here is Petri, the first "test-tube" rhesus monkey. The animal, delivered only minutes earlier, provided the first evidence that in vitro fertilization does not cause developmental disorders in rhesus monkeys.

Biological Materials and Resources Section

Developing models is an essential need in science and a key element of DRR's mission. Models can be important in understanding complex biological phenomena. Simpler systems, such as lower organisms, tissues and cells in culture, and nonliving systems, can sometimes be used to answer questions about universal biological processes. These systems are an inexpensive data source and may sometimes be acceptable alternatives to using higher animals in biomedical studies. The Biomedical Research Models Program was organized to encourage the development and evaluation of research techniques that use these simple organisms and nonliving models.

Some of these models already play an important part in NIH-supported research. For example, invertebrates are used to study the degradation of vitamins in the body, the control of enzyme biosynthesis, the toxicity of metal ions, and some forms of liver cancer. Assays based on cell and tissue cultures help improve understanding of physiological processes, and insects and nematodes are employed in basic studies of biology, biochemistry, and genetics in aging.

During 1984 an evaluation of the relevance and limitation of these model systems was conducted by the National Academy of Sciences under contract with DRR. On the basis of the NAS study and associated workshops, the Biomedical Research Model Development Program will begin awarding grants to outside investigators in 1985. A report on trends in the use of biological systems as models in biomedical research was prepared by the AR Program for the NAS steering committee. The Office of Technology Assessment used the report for its study for the Congress on alternatives to animal testing and experimentation. The Environmental Protection Agency requested copies as background material for their study of short-term bioassays and their impact on future regulatory policy.

Special Meetings and Reports

The *NIH Guide for the Care and Use of Laboratory Animals* was revised in 1984 and will be available in 1985. The ILAR committee which prepared the booklet took into consideration a variety of opinions expressed at three public hearings on animal care, as well as documents submitted by the animal welfare community and research scientists.

In 1984 there were also eight meetings of the Trans-NIH Coordinating Committee on Research Animal Resources. The meetings provided the NIH staff with an exchange of information on laboratory animal use data, regulation of the use of laboratory animals, activities of animal protectionist organizations, proposed changes in NIH policy regarding research animals, and related Federal legislation.

The AR Program held a forum in Seattle, Washington, on SAIDS and other immunodeficiency syndromes during the late spring of 1984. Investigators from the seven PRC's attended the meeting, a follow-up to one held at the Delta PRC in December 1983. Researchers reported on the virology, immunology, pathology, epidemiology, and diagnostic methods for studying the debilitating and often fatal disease SAIDS. Further meetings were planned for 1985.

Future Directions

The Regional PRC's will begin new studies on the epidemiology and pathology of SAIDS. In collaboration with virologists at NIH and other institutions, the centers will work toward developing diagnostic tests for the agent that causes SAIDS, possible vaccines, and other means of controlling the disease. Because the two syndromes are so similar, SAIDS studies will have direct relevance to research on human AIDS.

The PRC's will continue their efforts to renovate and restore their facilities. Breeding endangered and rare primate species will also continue. As the loss of natural habitats to farmland accelerates, it is crucial for the future of biomedical and behavioral research to preserve the dwindling populations of these species. Finally, the centers will continue to share their resources with interested investigators in the region.

The LASP will maintain its support for projects aimed at the causes, symptoms, diagnosis, and control of major diseases of laboratory animals. Projects will focus on viral diseases in rodents due to the large numbers of these animals used in research and the devastating impact of infections. The number of animal model and special colony projects has decreased in recent years, and responsibility for primate breeding activities will continue to be shifted to private industry.

Minority Biomedical Research Support Program

Program Description

The major goal of the Minority Biomedical Research Support (MBRS) Program is to help increase minority representation in biomedical research by promoting minority faculty and student participation and strengthening biomedical research capabilities at eligible institutions. These activities are helping to develop a cadre of minority scientists who will make significant contributions in the health sciences.

The MBRS Program, begun by DRR in 1972, funded projects in 1984 at 81 universities, colleges, and health professional schools with a total budget of $21,878,999. The program focuses on those schools in which 50 percent or more of the students are minorities; other institutions with a substantial, but less than 50 percent, minority enrollment that demonstrate special commitment to minority faculty and students are also included. MBRS funds in 1984 supported 4 grants that primarily serve American Indians, 47 that serve blacks, 5 that primarily serve Puerto Ricans, and 2 that serve Hawaiians. The remaining funds provide grants for a mixed population of minorities in major cities and the Southwest. Five new MBRS programs were begun in 1984.

In 1984 the MBRS Program assisted 1,020 undergraduate and 388 graduate students engaged in research projects, and aided 736 faculty in pursuing their biomedical research interests or in developing their research capabilities. At the annual MBRS symposium, hundreds of students presented research papers and posters on original work in which they had participated.

The Program collaborates with most of the institutes of the National Institutes of Health (NIH), the National Institute of Mental Health, and the National Institute of Alcohol Abuse and Alcoholism to cofund research projects at MBRS-supported facilities. The purpose of

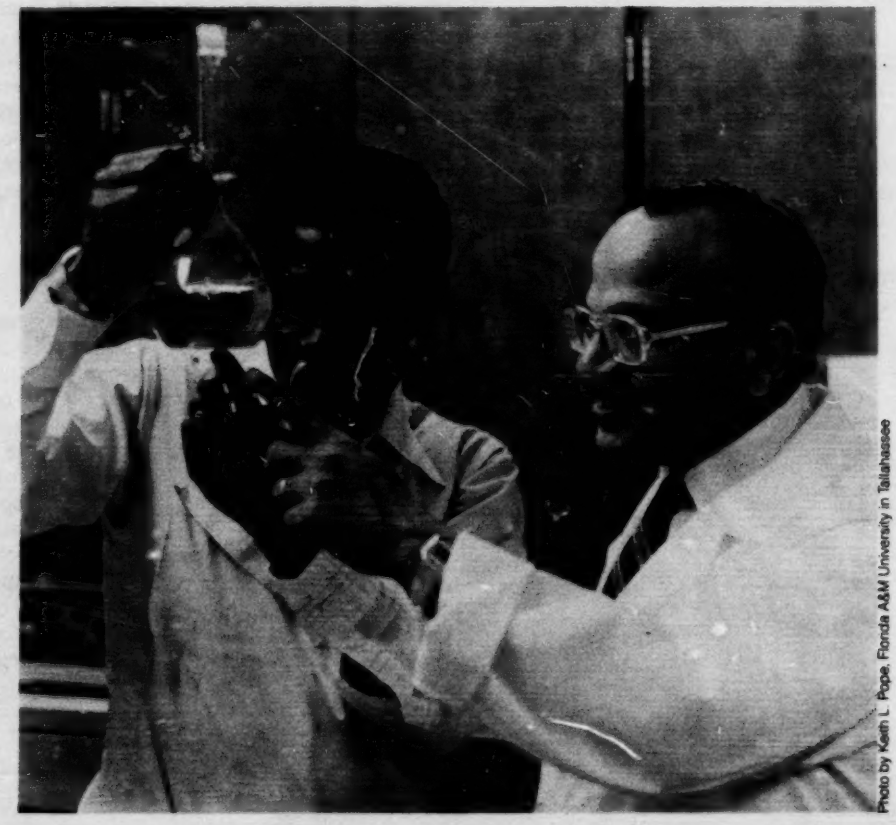


Photo by Keith L. Pope, Florida A&M University in Tallahassee

A faculty member involved in MBRS research (right) and a graduate student perform an assay to detect the presence of enzymes that alter the level of acetylcholine in the brains of diabetic rats. In 1984 more than 736 faculty members participated in 645 research projects funded by the MBRS Program.

cofunding is to help MBRS institutions and investigators ultimately to compete for NIH grants through the regular individual research grant programs. By 1984 cofunding support was extended to 206 biomedical research projects (compared to only 8 in 1975) and totaled $10,099,115.

Program Highlights

Institutional Development

Approximately 645 research projects, on a broad range of topics, from the study of a virus-carrying mosquito to an investigation of the secondary effects of diabetes, were conducted at MBRS-supported institutions in 1984. These studies included the 206 projects cofunded by the NIH and ADAMHA Institutes. The large number of projects overall indicates the degree of the impetus provided by the MBRS Program to scientific activity at grantee institutions. Many of these institutions were conducting only limited biomedical research prior to inauguration of the MBRS program.

Program support for state-of-the-art research equipment and other research resources, for hiring more research-oriented faculty, and for workshops to improve faculty grantsmanship skills has helped advance the participation of minorities in medical research. The special MBRS supplemental instrumentation grant program begun in 1983 has enabled institutions to purchase a variety of laboratory instruments including microscopes, spectrophotometers, spectrometers, and ultracentrifuges.

Faculty and Student Development

Since the program began, about 7,600 minority students have participated in MBRS-sponsored research. The program has graduated nearly 5,000 students. More than 80 percent have entered graduate schools, medical, dental or other health professional schools, and health-related careers. Of 586 MBRS students who graduated in 1983, the latest year for which data are available, 21 were accepted to dental school, 143 to medical school, 191 began graduate school, and 135 planned to continue education in the health field. Most students who did not pursue advanced degrees had jobs in the health area. In 1984 more than 1,400 MBRS students participated in MBRS research projects and attended science meetings and symposia. Many students made scientific presentations at these meetings, and some coauthored research papers.

On the basis of the results of a survey of the National Academy of Sciences, DRR has begun to record the number of Ph.D. recipients with MBRS support who graduated during the years 1974-1982. Initial reports show that during that period 118 students supported by the program earned Ph.D's, 116 of them in science or engineering fields.

Certain institutions have been particularly active in the MBRS Program: at Catholic University in Puerto Rico, for example, 193 undergraduates have participated in the program. Many are pursuing advanced degrees; 16 have already become physicians, 3 have become dentists, and 9 have the Ph.D. degree or are in Ph.D. programs. Another such program is at Xavier University in New Orleans, where 244 students received MBRS support between 1972 (when the program began) and 1983. MBRS graduates of the university include 22 physicians, 7 dentists, 2 Ph.D.'s, 1 optometrist, and 19 medical technologists.

MBRS faculty continued to refine their research skills and increase their contributions to biomedical research during the year. As a result of MBRS Program efforts, 63 faculty investigators have been awarded regular NIH research grants since 1972. In 1984, 26 MBRS faculty were members of NIH advisory and review committees, compared to only 3 in 1973. Ten former MBRS students who earned Ph.D's and completed postdoctoral training are currently MBRS principal investigators.

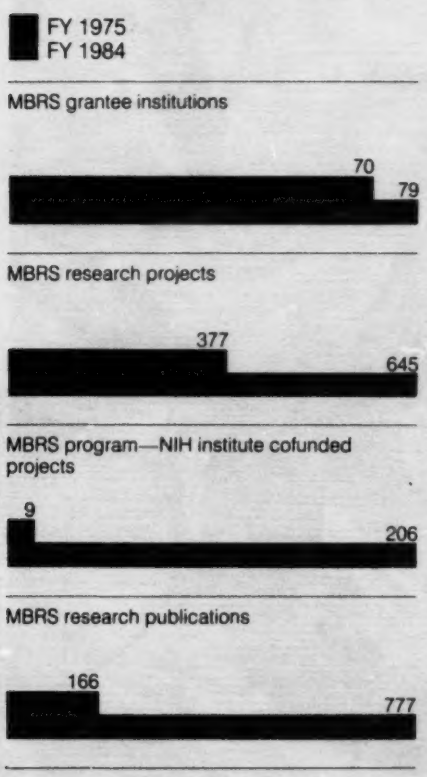
Research Accomplishments

Diabetes in Rats. At Florida A&M University, a pharmacology professor and collaborating MBRS graduate students have found preliminary evidence that diabetes adversely affects the nervous system of rats by interfering with the production of two enzymes, acetylcholinesterase (AChE) and choline acetyltransferase (ChAT). Both of these enzymes regulate acetylcholine, a neurotransmitter vital to the nervous system.

In rats with drug-induced diabetes, the investigators detected abnormal levels of these enzymes in the cerebellum, cerebral cortex, medulla oblongata, and other areas of the brain. Diabetes apparently stimulates the production of both enzymes as the animal system attempts to maintain a normal level of acetylcholine. But after a few days the balance can no longer be maintained, and the acetylcholine level becomes exceptionally high.

Overproduction of the ChAT enzyme has been correlated with higher-than-normal levels of acetylcholine. Studies in humans have linked high levels of the neurotransmitter

Minority Biomedical Research Support Program Accomplishments



to depression, and investigators have also linked diabetes to depression. Other neurological disorders are also common among long-term diabetics.

The long-range goal of this project is to find a drug therapy that reduces production of the ChAT enzyme and alleviates some of the adverse effects that diabetes has on the nervous system. If such a drug is discovered through research on rats, it may be tested in humans.

Possible Mosquito Host for Dengue Virus. MBRS students in Puerto Rico are helping scientists from the San Juan Laboratories of the Centers for Disease Control (CDC) study a mosquito that may be an unrecognized host for dengue fever viruses. Researchers at the CDC believe that the mosquito *Aedes mediovittatus* may maintain the dengue viruses during the long period between epidemics. When epidemics of dengue fever strike in the Caribbean, thousands of people develop the severe, but rarely fatal, influenza-like symptoms. Severe pains in the head, eyes, muscles, and joints, often lasting up to a week, are common.

Although the dengue viruses have not yet been isolated from *A. mediovittatus* in the wild, the mosquito readily transmits the viruses to offspring in the laboratory and has a natural habitat similar to a known carrier, *Aedes aegypti*. One MBRS student involved in the research is examining the genetic structure of *A. mediovittatus* by studying 32 isoenzymes in the mosquito. Using electrophoresis to separate different isoenzyme bands, he hopes to identify genetic variations among different populations and detect genetic markers for those mosquitoes that may be hosts for the dengue viruses.

Photo by Keith L. Pope, Florida A&M University in Tallahassee

An MBRS graduate student (right) assists a faculty member in dissecting portions of the brain of a diabetic rat. Their research, conducted at the Florida A&M University College of Pharmacy in Tallahassee, tracks the effect of diabetes on two brain enzymes that control levels of acetylcholine, a vital neurotransmitter.

Photo courtesy of Dr. Robert Novak, San Juan Laboratories, Centers for Disease Control

Aedes aegypti *may be only one vector of the virus that causes dengue fever, an influenza-like illness prevalent in the Caribbean. Researchers from the Centers for Disease Control, aided by MBRS graduate students in Puerto Rico, have shown in laboratory studies that another species of mosquito closely related to* A. aegypti *also carries the virus.*

Workshops and Conferences

About 1,500 students and faculty participated in the 12th Annual MBRS Symposium, held in Washington, D.C., during April 1984. Students presented more than 570 research papers and poster displays. Lectures on hypertension, AIDS, nutrition and aging, and infant behavior were featured at the conference, as well as hands-on workshops on electron microscopy and high-performance liquid chromatography.

At the annual MBRS Program Directors' meeting, also held in Washington, D.C., during the spring of 1984, talks focused on how institutions can improve their grant applications and on strategies for meeting program needs in the 1980's. Discussions at the meeting also centered on four MBRS initiatives that had been proposed by the MBRS advisory council.

In September 1984, as an aid to implementing a new funding program directed to undergraduate colleges, the MBRS Program sponsored a special grantsmanship workshop in Atlanta. Forty-one officials from 38 eligible institutions were informed about the new initiative, the NIH peer review process and the elements of a good grant proposal.

Future Directions

Members of the National Advisory Research Resources Council work group on the MBRS, along with several MBRS program directors, General Research Support Review Committee members, and other representatives of the minority research community, met in a retreat in September 1983 to review MBRS program goals, discuss policy and management issues, and develop recommendations for the future. The new program initiatives outlined below emanated from these discussions.

To help meet the goals defined for MBRS in the mid-1980's, two new initiatives suggested by MBRS advisory groups for inclusion among MBRS activities in 1985 were:

☐ ***A new program will be established to encourage participation in biomedical research at undergraduate colleges that have substantial enrollments of minority students but are not funded by the MBRS Program.*** Many of these small, predominantly minority institutions have had limited success in competing for sustained MBRS support. This initiative will provide a mechanism to involve such institutions in the effort to increase the number of minorities who pursue biomedical research careers. Historically, black colleges have awarded 40 percent of the baccalaureate degrees earned by black students, although these colleges enroll only 17 percent of all black college students throughout the nation. Inadequate budgets and other factors have hindered the use of funds to develop and support the resources needed to encourage scientific research at these colleges. At the same time, unusually high faculty teaching loads have deterred faculty research productivity. Up to $1 million will be available to support research efforts at minority undergraduate colleges in 1985, and it is expected that 10 awards can be made.

☐ ***In 1985 up to $1 million will be available to the MBRS Thematic Project Grant (TPG), a new activity intended to respond to the increase in scientific research that has occurred in some MBRS institutions since the Program was established in 1972.*** By now some MBRS institutions with graduate programs have acquired a critical mass of biomedical research faculty and have expanded and updated their biomedical research resources. These institutions are capable of developing greater faculty and interdisciplinary collaboration on specific research themes. The Thematic Project Grant is intended to support this type of research effort. It is another transitional step toward regular NIH grant support, and it is expected that three to six TPG awards can be made in 1985.

Biomedical Research Support Program

Program Description

The DRR Biomedical Research Support (BRS) Program is designed to strengthen institutional research in the health sciences. It consists of three grant programs: the Biomedical Research Support Grant (BRSG) Program, the Shared Instrumentation Grant (SIG) Program, and the Minority High School Student Research Apprentice (MHSSA) Program.

The BRSG Program, begun in 1960, provides a pool of flexible funds to institutions conducting health-related research for self-determined needs not usually met by Public Health Service (PHS) project grants. Each research center determines how the funds will be used to improve its programs. The SIG Program, a subprogram of BRS founded in 1982, provides institutions with costly research instruments not readily available through other NIH grants. These instruments are shared by several NIH-supported investigators at the facility. The MHSSA Program, authorized in 1980, offers apprentice-level research positions to 666 minority high school students for 8 weeks during the summer to foster their interest in biomedical research careers.

Biomedical Research Support Grant Program

Giving research centers the opportunity to allocate funds enables them to respond quickly to unexpected needs or a sudden change in research emphasis, and to explore in pilot projects the scientific validity of new theories or techniques. As research progresses, investigators may suddenly need to learn new skills, a promising project may be without funds between grants, or a new idea may merit exploration. The flexible funds of the BRSG Program complement or supplement PHS research project grants by providing for short-term, emergency, low-cost, interim, and shared research resource needs not readily covered by the project grants. Establishing new laboratories, bolstering research opportunities for minorities and women, and upgrading facilities to meet standards for animal care are other activities supported by the BRSG Program.

U.S. health professional schools, academic institutions, hospitals, and nonprofit research organizations are eligible for the awards if they have received at least three PHS biomedical or health-related behavioral research grants totaling $200,000. BRSG awards are not given directly to individual investigators. Research centers may use the funds for shared resources or to support new investigators or pilot research projects.

Pilot Research. Pilot studies test the scientific validity of new ideas, encourage the use of innovative techniques, and reduce the risk of major cost commitments to projects that might prove unproductive. The results of such studies may be important to investigators, regardless of outcome: new information may prompt a new direction in research or justify further funding of the projects.

In 1984 BRSG-funded pilot research projects included a model of inner ear changes in ferrets with Reye syndrome, a disease that can be fatal in children. Reye syndrome occurs after a brief viral illness, usually influenza or chickenpox. But because influenza infection precedes the diagnosis of Reye syndrome, its role and interaction with other agents, such as aspirin, in causing the syndrome is difficult to study in patients. The

FY 1984 Biomedical Research Support Grants by Type of Institution

Type of Institution	No. of Grants	Amount
Schools of medicine	123	19,004,938
Other health professional schools	100	4,454,500
Other academic institutions	164	12,885,944
Hospitals	68	4,748,345
Health departments	2	104,084
Research organizations	89	5,929,189
	546	$47,127,000

Photo courtesy of R.W. Van Devender

BRS-supported researchers have found that the venom of western diamondback rattlesnakes may yield an agent for dissolving blood clots, a suspected cause of heart attacks.

ferret is a potentially good animal model because it is highly susceptible to human influenza virus.

Researchers recently linked findings from an earlier BRS pilot study in rats to explain the unexpected deaths of low-birth-weight infants. The rats had been fed unusual diets and later developed fatty livers. A similar condition had been noted among the infants who died, and researchers who examined both the rat and human infant studies have implicated a new vitamin E supplement as a cause of the infant deaths. The FDA subsequently banned the supplement and Congressional hearings were held. The original pilot study in rats was at a histopathology research laboratory in a southern medical school. The laboratory's main resource, a transmission electron microscope, was purchased with BRS funds.

Regular Projects. The purpose of BRSG support for an established project is to provide funds for an unexpected requirement or the opportunity to pursue a new line of research. Regular projects are conducted by investigators who have already participated in sponsored research.

Interim Funding. In contrast, interim support is provided to scientists who are not currently engaged in sponsored research. A typical recipient would be a researcher who needs funds to maintain an animal colony during the time between receipt of grants for NIH-sponsored projects. Such emergency funding saves research projects from being interrupted or abandoned before completion. BRSG funding also becomes critical during temporary interruption of PHS grant support, keeping the staff on the project and preventing the need for costly reassembly of staff or training of a new research team when standard support resumes.

Central Resources. Central resources such as equipment and research facilities are expensive, especially in comparison to the lesser funds needed to support pilot studies and other projects. BRSG helps fund such major resources by allowing institutions to carry forward funds from one year to the next, a provision that permits research centers to plan the purchase of expensive equipment without interrupting funding of smaller projects. BRSG support of central resources usually requires a collaborative effort among several investigators and departments who will benefit from the purchase. Central-resource funding may also provide laboratory equipment at an animal research facility or upgrade the center.

Complement to Other Research Funding. In some instances, partial funding for a research project is available from one or more sources; BRSG funds are used to complete the project for which use of other funds may be inappropriate or unavailable.

Recruitment. Recruiting talented scientists strengthens the capabilities of any research center. BRSG funds can be used to quickly provide equipment and other resources to these scientists, a factor that may attract investigators to a new research program.

Research Highlights

The BRSG Program directly supported over 9,000 pilot and regular research projects at 546 institutions in 1984. The program indirectly supported an undetermined number of projects through BRSG-funded, centrally shared resources and facilities. The following research highlights demonstrate the impact of BRSG awards on research productivity.

Exercise and Asthmatic Children. The type of exercise best suited for asthmatic children has long been debated among physicians. Some who believe vigorous exercise may cause exercise-induced bronchospasms (EIB) recommend only short-term activity for asthmatics, while other doctors encourage all forms of exercise as long as immediate drug treatment for an asthma attack is available. But recently a joint BRSG-supported study at the Children's Hospital of Los Angeles and the Children's Hospital Medical Center of Northern California found that fitness and cardiovascular function improved in 15 asthmatic children who followed a 6-week running program, with no increase in asthma attacks or EIB. The bronchospasms that did develop in about half the children were no more severe than attacks that occurred following a bicycle stress test used to evaluate the children before the exercise program began. The researchers believe that the results of their study, in which the children ran 2 miles, four times a week, can also apply to adults with asthma. Such an exercise regimen will not overcome the psychological barriers associated with asthma but appears to improve the overall health of asthmatics.

New Technique for Manufacturing Monoclonal Antibodies. A new technique for producing human monoclonal antibodies has enabled researchers to produce in animals antibodies to tetanus and diphtheria toxins and *Hemophilus influenzae,* a common cause of meningitis in young children. Monoclonal antibodies are usually made from mouse lymphocytes that are fused to mouse myeloma cells, tumor cells that reproduce rapidly. The resulting hybrid, or hybridoma, can manufacture large quantities of mouse antibodies to specific infectious agents. But in humans these antibodies sometimes cause side effects,

and human cell hybridomas are often difficult to produce. In the new technique, studied at St. Jude Children's Hospital in Memphis, Tennessee, human peripheral blood lymphocytes are collected shortly after an adult is injected with infectious material or a vaccine active against infection. The material temporarily spurs the supply of antibody-producing B lymphocytes, increasing the chances of having a successful hybridoma. Monoclonal antibodies derived from hybridomas made with the new technique have protected animals against diphtheria, tetanus, and meningitis; the antibodies have not yet been tested in humans.

Pets Signal Human Health Risks. Because pets often share the same environment as their owners, diseases in pet dogs caused by environmental factors may indicate a human health risk, according to researchers at the University of Pennsylvania School of Veterinary Medicine. The investigators correlated asbestos exposure in dogs to the spontaneous development of mesotheliomas, tumors that attack membranes lining internal body cavities. Researchers identified possible sources of asbestos exposure for 12 of 16 dogs in their study; many of the owners worked in shipyards or at jobs where exposure to asbestos was high or used asbestos materials in a hobby. Other studies have shown that shipyard workers are likely to be exposed to asbestos and have an increased risk of developing mesothelioma. Tumors associated with asbestos, the researchers say, take only 5 to 6 years to develop in dogs, but may take 20 to 40 years in humans. Detection of cancer in pets, therefore, may allow physicians to identify people who are exposed to asbestos and who are at risk for developing the same cancer. Medical examination revealed that one pet owner already had pleural scarring of the lung, a benign condition associated with asbestos exposure. The researchers advise that people exposed to asbestos should have periodic chest X rays for early detection of lung cancer and should avoid smoking to lessen their chances of developing the disease.

Snake Venom and Blood Clots. Venom from the western diamondback rattlesnake, one of the deadliest snakes in the United States, may yield an agent for dissolving coronary bloodclots, a suspected cause of heart attacks. Researchers at the Temple University School of Medicine have shown that a still unidentified agent, present in small quantities in the venom, breaks down clotting factors in human blood through a three-step cellular reaction. Because of the agent's indirect action, scientists believe that it can marshal the body's natural ability to destroy coronary bloodclots. The venom component does not itself break down fibrin, the plasma protein that consolidates bloodclots. Instead, the researchers say, the venom agent stimulates human cells to produce compounds that decompose fibrin. By isolating and administering the potent venom component in minute, nontoxic amounts, the investigators hope to have a substance that can safely regulate the body's mechanism for combatting bloodclots.

BRSG Evaluation. An evaluation of the BRSG program requested by the Government Accounting Office affirmed its value for institutions receiving BRSG grants and for research programs sponsored by NIH. The study found that the program's emphasis on decentralized disbursement of funds enables institutions to easily strengthen specific areas of research and aids in developing future research strategies. BRSG funds were found to be highly coveted by administrators and investigators because of their flexibility and quick-

Photo courtesy of the USDA Food and Nutrition Service

Vigorous exercise improves the fitness of asthmatic children and does not increase the frequency of asthma attacks. The study of children with asthma is just one of 9,000 research projects supported by the BRS at 546 institutions during 1984.

Photos courtesy of Dr. L.T. Glickman

Shown here is diseased pleural tissue (bottom) from a dog (top) that subsequently died of mesothelioma. BRS-supported research has shown that environmentally caused disease in pets may signal a health risk for owners who share the same environment.

turnaround time. No evidence was found to suggest that a more restrictive definition of how BRSG funds are used would increase Program performance; if anything, results of the study suggested that restrictions could be counterproductive.

Shared Instrumentation Grant Program

State-of-the-art instruments have become increasingly important in biomedical research. But equipment such as mass spectrometers and electron microscopes may be prohibitively expensive for many laboratories; the objective of the Shared Instrument Grant (SIG) Program is to provide sophisticated research instruments that will be shared among NIH-supported investigators. The program began in 1982, funding 23 awards for a total of $3.7 million. In 1984 the number of awards had increased to 115 for a cost of $19.7 million.

Research groups of three or more NIH-funded scientists from any organization that receives BRS grants are eligible for SIG funds. Applications are considered only for instruments that cost at least $100,000; the maximum award is $300,000, although the equipment cost may exceed that amount. In contrast, many NIH project grants provide funds only for standard research instruments typically costing $20,000. Unlike the DRR Biomedical Research Technology Program, which awards grants to develop sophisticated biomedical technology resources, the SIG provides capital only for the purchase of already available instruments.

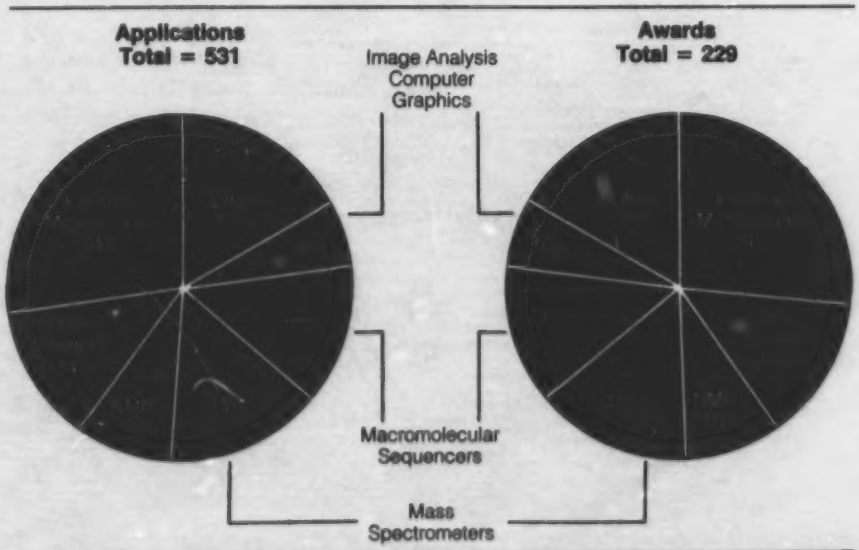
SIG awards are made only for the direct costs of acquiring new or updating existing research instruments. Costs for placing the instrumentation in working order as well as associated maintenance, support personnel, and service costs are paid by the grantee institution. Image analyzers, cell sorters, electron microscopes, and mass spectrometers are some of the instruments that the SIG program provides to NIH-supported investigators.

Resource Description

A cell sorter that can count thousands of cells per second and collect microscopic droplets of single cells is one of the SIG-supported resources. Another resource is an autoradiographic system in operation at the Washington University School of Medicine in St. Louis. The imaging system scans slides, autoradiograms, and electrophoretic gels among other materials to visually detect data that may indicate the efficiency of blood flow, glucose use, or drug receptor interaction. A digitizing head shines light through or onto the material and collects more than 4 million data points, which are stored on a computer. An image processor translates and displays this information on a color monitor.

Scientists use the instrument to study the brain, the heart, and muscles, as well as subtle changes in cell cultures. The entire human body can be studied; researchers in rehabilitation medicine use the instrument to scan photographs of patients to determine how well they are recovering from stroke or arthritis, for example. The image analyzer allows the physician to precisely determine healing progress over a period of time.

Biomedical Research Support Shared Instrumentation Grant Program Application and Award Distribution, FY 1982-84 by Type of Instrument



SIG Assessment

To determine the types of equipment requested and the need for large-scale instruments, a 3-year assessment of the SIG program was recently completed. Medical schools and graduate schools accounted for the largest number of instrument requests, up from 68 percent of total applications in 1982 to 81 percent in 1984. The six instruments most frequently requested were electron microscopes, cell sorters, nuclear magnetic resonance spectrometers, mass spectrometers, macromolecular sequencers, and image analysis/computer graphics systems. Electron microscopes were the single most popular item.

The study also found that the distribution of NIH research grants among SIG users has remained stable since the instrument program began. The National Cancer Institute; the National Institute of General Medical Sciences; the National Heart, Lung, and Blood Institute; the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases; and the National Institute of Allergy and Infectious Diseases are the major supporters of investigators with SIG awards.

*Titi monkeys at the primate research centers may provide a model for human stress response. Behavior of the monkeys (*Callicebus moloch*) has been linked to dominance of the parasympathetic nervous system and predisposition to immune system breakdown.*

Minority High School Student Research Apprentice Program

The Minority High School Student Research Apprentice Program (MHSSA) offers summer apprenticeships in biomedical research to minority high school students. The awards, $1,500 for each apprentice position, encourage young people to pursue careers in the health field. Although experience varies from laboratory to laboratory, students generally work on research problems, collect data, and report their findings in written papers and seminars. Many high school apprentices develop a close working relationship with graduate and undergraduate students.

Only research centers which received funds from the Biomedical Research Support Grant Program or the Minority Biomedical Research Support Program during the most recent fiscal year are eligible for the awards. Funds are awarded to the research institution rather than directly to students, but the money can only be used for student salaries, to hire additional apprentices, extend the period of apprenticeship, or enhance the research experience for students.

The program has grown steadily since its inception in 1980. In that year the MHSSA Program funded apprenticeships for 200 students at a cost of $400,000. During 1984 the MHSSA program funded 666 students at 284 institutions for a total of $1 million.

A program review by the National Advisory Research Resources Council and the BRS Program Branch prompted the MHSSA staff to revise its set of operating procedures. The recommendations, which were approved by the advisory council, suggested that the pool of eligible institutions for minority awards remain diversified and that, in selecting candidates, student motivation, ability, and accomplishments; teacher evaluations; and parental commitment should be considered. To develop and carry out a successful program for minority high school students it may be most effective to fund four to six students at each research institution, the staff suggested.

Future Directions

The MHSSA Program announced in 1984 that DRR will give preference in future funding to those research centers that can support five to six summer students, and provide institutional funds to complement DRR awards. This policy change is in accordance with recommendations from the National Advisory Research Resources Council. Final funding, however, may allow DRR support for only three or four students because of limited funds and an overall increase in the number of applications.

The SIG program plans to continue to strengthen the research capabilities of PHS-funded scientists by providing large-scale instruments for shared use.

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